Center for Clinical and Translational Science

Abstracts

Oral Presentation Session A

Abstract Title:	**Sexual Dimorphism in a Marfan Syndrome Mouse Model**
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Abstract: The effect of sexual dimorphism on aortic pathology in mouse models of Marfan Syndrome has not been defined. Therefore, we determined differences in aortic diameter expansion between sexes in fibrillin-1 hypomorphic (FBN1mgR/mgR) mice. Ascending aortic diameters from male and female FBN1mgR/mgR mice and their wild type littermates were assessed every 4 weeks from 6 to 18 weeks of age by ultrasound. Measurements were taken luminal edge to luminal edge in diastole. Differences in aortic diameters between male and female FBN1mgR/mgR mice were detected at 6 weeks of age. There were no significant diameter differences between sexes of wild type littermates. At 18 weeks of age, differences of aortic diameters between male and female FBN1mgR/mgR mice increased, while there were no significant differences between sexes of wild type littermates. External aortic diameter measured after termination at 18 weeks correlated with in vivo ultrasound measurements. Male FBN1mgR/mgR mice had significantly greater aortic dilation compared to their female littermates. In contrast, aortic diameters were not different between sexes of wild type littermates. In addition to increased aortic diameter, death due to aortic rupture by 18 weeks was more frequent in male FBN1mgR/mgR mice than in female FBN1mgR/mgR mice. FBN1mgR/mgR mice exhibit sexually dimorphic ascending aortic diameters as early as 6 weeks of age. This sex difference increased with age in FBN1mgR/mgR mice, while their wild type littermates do not exhibit significant difference. Subsequent studies using this model of Marfan Syndrome should state the sex of mice.

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Center for Clinical and Translational Science

Abstracts

Oral Presentation Session A

Abstract Title:	**Diet High in Fat and Salt Recapitulates the Type 2 Diabetes-Predictive Human Th17 Cytokine Profile in Mice**
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Abstract: Inflammation plays important roles in type 2 diabetes (T2D) pathogenesis. We demonstrated one T-cell subset, Th17s, produce a cytokine signature that predicts T2D in people. The failure of animal models to recapitulate the dominance of Th17s in obesity-associated metabolic decline makes preclinical tests on roles for Th17s in T2D challenging. People become obese/T2D after years of diet simultaneously high in fat, simple sugars, and salt (NaCl), whereas mouse models of obesity use a diet rich in fat and simple sugars, but low in NaCl. Since NaCl promotes development of Th17 cells, we hypothesized that feeding mice a diet high in fat and salt would yield a mouse model that recapitulates the Th17-dominated inflammatory profile in human T2D. To test this hypothesis, we fed 6-week-old male C57BL/6 mice high fat/low salt diet (HFD, 0.5 % NaCl) or high fat + high salt diet (HSD, 2% NaCl) for 12 weeks. HFD and HSD mice were similar in body weight, glycemic control, motion and fat distribution. We sort-purified CD45+CD4+ splenocytes (helper T-cells) and stimulated cells with anti-CD3/CD28 for 40 hrs before measuring secreted cytokines. T-cells from HSD mice secreted more IL-17A, IL-17F, IL-22, IL-13 and GM-CSF, which approximate the human T2D-predictive Th17 signature. Comparison of cytokines from HFD and chow fed mice showed HFD didn't increase Th17 signature cytokines. Our data indicate that HSD mice recapitulate the Th17-predictive inflammatory signature of T2D, raising the possibility that this model could be useful for preclinical testing of Th17 blocking drugs like secukinumab for T2D pathogenesis.

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Oral Presentation Session A

Abstract Title:	**Neuroprotective strategies following severe controlled cortical impact traumatic brain injury: lipid peroxidation-derived neurotoxic aldehyde scavenging and inhibition of mitochondrial permeability transition**
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Abstract: Traumatic brain injury (TBI) represents a significant health crisis in the United States. Currently there are no neuroprotective FDA-approved pharmacotherapies for TBI. Due to the complex pathophysiology which occurs following TBI, more robust pharmacological approaches must be developed. Mitochondrial dysfunction and the formation of neurotoxic aldehydes contribute extensively to TBI pathology, making them promising therapeutic targets for prevention of cellular death and dysfunction following TBI. The following are evaluated. 1) The neuroprotective effect of cyclosporine A (CsA), on synaptic and non-synaptic mitochondria. Mitochondria are heterogeneous, consisting of both synaptic and non-synaptic populations, which have distinct properties. Our results indicate that compared to non-synaptic mitochondria, synaptic mitochondria sustain greater damage 24h following severe controlled cortical impact injury in young male rats, and are protected to a greater degree by CsA, an FDA-approved immunosuppressant, capable of inhibiting mitochondrial permeability transition. 2) The neuroprotective effects of a 72h subcutaneous continuous infusion of CsA combined with phenelzine (PZ), an FDA-approved monoamine oxidase inhibitor (MAOI) class anti-depressant capable of scavenging neurotoxic aldehydes. Our results indicate that individually CsA or PZ attenuate neurotoxic aldehyde formation, PZ maintains mitochondrial respiratory control ratio and cytoskeletal integrity, but together, PZ and CsA, do not maintain neuroprotective effects. 3) The ability of PZ (aldehyde scavenger and MAOI), to attenuate cognitive dysfunction following TBI compared to hydralazine (aldehyde scavenger) and pargyline (MAOI), in an attempt to further elucidate the role PZ's MAOI mechanism of action has in TBI pathophysiology.

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Abstracts

Oral Presentation Session A

Abstract Title:	**Remember Alzheimer's Disease When Evaluating White Matter Hyperintensities As a Marker for Cerebral Small Vessels Disease**
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Abstract: Objective: To examine how white matter (WM) alterations are associated with cerebrovascular disease (CVD) risk and/or CSF levels of beta-amyloid (A?1-42). Methods: Clinical measures of CVD risk, including hypertension was collected from 62 participants who also had CSF sampling and MRI scans. CSF level of A?1-42, which reflects presence or absence of Alzheimer's disease pathology, was measured and fluid-attenuated inversion recovery imaging and diffusion tensor imaging were obtained to assess white matter hyper-intensities (WMHs) and microstructural properties of normal-appearing WM (NAWM). Statistical moderation analyses investigated the relationships among hypertension, CSF A?1-42 levels, and WM alteration. Voxelwise analyses were performed to examine spatial patterns of WM alteration associated with each pathology. Results: Hypertension and CSF A?1-42 levels were each associated with WMHs and alterations in NAWM, as well as with each other. Moderation analyses demonstrated that neither hypertension nor CSF A?1-42 levels moderated the effect of the other on WM alteration. Furthermore, voxelwise analyses showed spatially distinct patterns of WM alteration associated with hypertension and CSF A?1-42 levels. A?1-42-associated WM alteration was primarily found in posterior parietal WM and near the anterior horns of the lateral ventricles, whereas hypertension-associated WM changes were primarily in the deep WM. Conclusions: Associations of CVD-risk and lower CSF A?1-42 levels with WM alteration were independent, rather than synergistic. These topographies may indicate distinct pathophysiologies underlying WM alteration. Understanding the degree of such spatial distributions may improve diagnostic accuracy and guide optimal development of treatment options that address each underlying pathology.

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Abstracts

Oral Presentation Session A

Abstract Title:	**Blood-Brain Partition Coefficient Correction Improves Gray-White Matter Contrast in Blood Flow Measurement in Mice**
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Abstract: Introduction: The blood-brain partition coefficient (BBPC) is an important parameter in the quantification of cerebral blood flow (CBF) as measured by arterial spin labeling (ASL) acquisitions. While this tissue-specific parameter is known to vary with age and brain region, particularly in gray vs white matter, the current consensus in the field of ASL is to assume a single constant value of 0.9mL/g for all regions and all subjects.1 In this study we use an accelerated calibrated proton density (ACPD) imaging technique2,3 to measure the BBPC directly, thus enabling a voxel-wise correction for BBPC when quantifying CBF. We then compare the BBPC-corrected CBF maps to standard maps calculated using the assumed constant value to test the hypothesis that BBPC-correction will increase the quality of quantitative CBF images. Methods: Imaging Protocol- Male C57Bl/N mice aged 12 months (n=8) were imaged using a 7T Bruker ClinScan (Bruker Biospin, Ettlingen, Germany) to acquire both ACPD images and pseudo-continuous ASL images. The ACPD images were acquired with a 39mm birdcage transmit/receive coil and the pCASL images were acquired with a four-channel phased-array surface receive coil without disturbing the position of the mouse by means of a custom bed and nose cone. For the ACPD images a series of phantoms with 0, 10, 20, 30, and 40% deuterium oxide in distilled water and doped with gadobutrol (Gadavist, Bayer Healthcare Pharmaceuticals, Whippany NJ, USA, 0.07mM), along with a blood-sample obtained from the facial vein of the mouse were placed inside the volume coil. A series of image stacks were acquired with a phase-spoiled, FLASH-GRE sequence (FOV= 2.8cmx2.8cm, matrix= 256x256, slice thickness= 1mm, number of slices= 10, flip angle= 90°) with a very short TE (3.2ms) and 6 different TR values (125, 187, 250, 500, 1000, 2000ms). The pCASL images were acquired with FOV= 1.8cmx1.3cm, matrix= 128x96, slice thickness= 1mm, number of slices= 6, TE/TR= 20/4000ms, label duration= 1.6s, post-label delay= 0s, averages= 120. Image Analysis- The centermost 2 slices containing the hippocampus were selected for analysis. The brain regions of the ACPD and pCASL images were isolated independently using an automated skull-stripping algorithm and then coregistered. The BBPC map was then calculated voxel-wise by fitting the ACPD series to the mono-exponential recovery curve S= M0*[1-e^(TR/T1)] to yield a map of M0, normalizing to the phantom series, and finally using the equation BBPC= M0,brain/(M0,blood *1.04g/mL).2 Quantitative CBF maps were calculated from the pCASL images according to the equation, where PLD is post-label delay, LD is label duration, T1,blood is the longitudinal relaxation of blood (2.2s at 7T), and ? is label efficiency (0.85). For standard CBF maps the BBPC was assumed to be a constant 0.9mL/g while the corrected maps used the measured BBPC maps to calculate CBF. Regions of interest encompassing the motor and sensory cortex, corpus callosum, and hippocampus were drawn manually on each analyzed slice. BBPC, uncorrected CBF, and corrected CBF values were averaged for each region of interest. Gray-white contrast was determined for each slice as the difference of average CBF values in gray and white matter regions of interest. All analysis was performed with self-written scripts in Matlab (Mathworks, Natick, MA, USA). Results: BBPC maps demonstrate significantly elevated BBPC in the cortical region (μCtx= 0.99±0.04mL/g) relative to the corpus callosum (μCC= 0.93±0.05mL/g, p = 0.008) and the hippocampus (μHc= 0.95±0.04mL/g, p= 0.057) (see Figs. 1&2). The corpus callosum always displayed lower CBF (μuncorrected= 1.44±0.3mL/g/min, μcorrected= 1.51±0.4mL/g/min), than the cortex (μuncorrected= 2.81±0.4mL/g/min, μcorrected= 3.09±0.5mL/g/min, p<0.001) and the hippocampus (μuncorrected= 2.90±0.6mL/g/min, μcorrected= 3.07±0.7mL/g/min, p<0.001) (see Fig. 3), however the uncorrected CBF maps underestimated blood flow in the cortex by 9.3% (95% CI= 5.6-12.9%), the corpus callosum by 4.9% (95% CI= 1.1-8.6%), and the hippocampus by 6.0% (95% CI= 2.5-9.5%) compared to the corrected CBF (see Fig.4). Correcting for regional differences in BBPC thus improves gray-white matter contrast by 15.1% in the cortex (95% CI= 10.1-20.1%) and 7.0% in the hippocampus (95% CI= 2.4%-11.7%). Discussion: In this study we measure significant regional differences in the BBPC of mice. These regional differences translate to errors in CBF quantification when using a global, constant value as is currently the standard in ASL imaging. Those errors are particularly important when studying white matter pathologies in diseases such as multiple sclerosis, leukoaraiosis, and Alzheimer's disease as the gray-white matter contrast can be reduced by as much as 15% by failing to account for the reduced BBPC of white matter relative to gray.

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Oral Presentation Session A

Abstract Title: **Non-Contrast Retinal Video Processing for Visualization of Blood Flow**

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Abstract: Alterations in blood flow are the hallmarks of many diseases. The National Eye Institute has identified the need to engineer and apply new techniques to study blood flow in the retina and choroid. We propose the use of computer vision and video processing to elucidate the role of the choroid in retinal pathologies that involve abnormal perfusion. To this goal, we describe an innovative technique by which retinal and choroidal blood flow can be visualized and quantified without the use of contrast dyes or specialized equipment. Preliminary retinal video obtained from a surgical retina video library demonstrates visualization of choroidal perfusion after being processed with our technique. Plotting signal intensity versus time reveals a pulsatile-like waveform. Videos of the hand and arm were recorded while vessels were occluded via a blood-pressure cuff and slowly unoccluded, using consumer-grade digital video cameras. After enhancement, signal intensity and amplitude of revealed pulsations increases while pressure decreases, correlating with increased blood flow. Simultaneous pulse-oximetry served as ground-truth signal. Retinal videos of a healthy subject were taken using an analog fundus camera modified to support digital cameras. Our software enhancement enables increased visibility of choroidal vasculature while also having a reproducible quantification (ICC = 0.840, 95% CI = 0.530-0.981).

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Abstracts

Oral Presentation Session B

Abstract Title:	**Impact of Posttraumatic Stress Symptoms on Physical Health Complaints among College Women: Indirect Effect of Sleep Quality**
Author(s):	M. F. Hazlett, Department of Psychology, U of Kentucky C. O. Hood, Department of Psychology, U of Kentucky C. L. Badour, Department of Psychology, U of Kentucky

Abstract: Background. Individuals with posttraumatic stress symptoms (PTSS) frequently report physical health complaints. The relation between PTSS and health problems may be indirectly related through sleep quality. Thus, this study examined whether PTSS had an indirect effect on physical health complaints via reduced sleep quality. Method and Hypotheses. The cross-sectional survey included trauma-exposed women (N=491, Mage=18.83, SD=1.06) who responded to items assessing past-month PTSS (PCL-5), sleep quality (PSQI), and physical health complaints (PHQ-15). Past-week severity of depression, anxiety, and stress was also assessed (DASS-21). We hypothesized that PTSS would be associated with health complaints via reduced sleep quality. Results. An indirect effect model was tested. Analyses controlled for DASS-21 total scores. The total effect of PTSS on physical health complaints (path c: B=0.04, SE=0.01, p=.002) was significant. PTSS were positively associated with poorer sleep quality (path a: B=0.04, SE=0.01, p=.001). Poor sleep quality was positively associated with increased physical health complaints (path b: B=0.50, SE=0.06, p<.001). The indirect effect of PTSS on physical health complaints (path ab: B=0.02, SE=0.01, BC 95% CI [0.008, 0.03]) was significant. Additionally, PTSS were no longer significantly related to physical health complaints (path c': B=0.02, SE=0.01, p=.08) after accounting for sleep quality. Thus, PTSS are related to physical health complaints, in part, by way of sleep quality. Conclusion. This study offers evidence that PTSS are related to physical health complaints by way of poorer sleep quality. Therefore, sleep quality may serve as an intervention target for alleviating physical health complaints among trauma-exposed women.

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Oral Presentation Session B

Abstract Title:	**Contextualizing the Stress Experience of Custodial Grandparents in Central Appalachia**
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Abstract: With escalating rates of parental substance abuse, addiction, and incarceration in the rural U.S. and elsewhere, grandparents increasingly have stepped in to fulfill childrearing responsibilities. The rate of custodial grandparenting has been especially widespread in rural Appalachia, a region with sparse resources. The shift in kinship care reflects the resiliency and utility of extended family structures in Appalachia, but presents new challenges, including increased stress, for grandparent wellbeing. To better understand the stress experience of rural Appalachian grandparents with primary childrearing responsibilities, we conducted twenty-six in-depth interviews. Interviews were transcribed, subject to content analysis, and co-coded with 80% inter-coder reliability using NVivo11. Stress was described as arising from repositioning to parental role and forfeiting the grandparenting role, and from interactions with the parent generation. Physical health and worry about the ability to physically and financially provide for grandchildren were further sources of stress. Despite these sources of stress, grandparents suggested that caregiving was a major protective factor against depression and beneficial for their health and activity levels. Moreover, many grandparents indicated a cultural and historical continuity of grandparenting in a culture that traditionally has emphasized extended family ties and extensive social support.

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Oral Presentation Session B

Abstract Title:	**Greater Changes in Acute Renal Function for African American Total Knee Arthroplasty Patients**
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Abstract: Race has been identified as a risk factor for related to complication and readmission rates after primary total knee arthroplasty (TKA.) African American patients have been shown to be at greater risk of renal disease due to higher rates of comorbidities. It remains unclear if racial differences in acute renal function exist following primary TKA. Our purpose in this retrospective study was to compare pre-to-postoperative change in serum creatinine between African American and Caucasian TKA patients. We hypothesized that African Americans would demonstrate significantly greater changes in serum creatinine, and a significantly greater proportion of African Americans would demonstrate creatinine changes consistent with acute kidney injury (AKI). Patients were excluded if pre- and postoperative serum creatinine values were not included in their EMR. None were excluded based on sex, age, BMI, preoperative diagnosis or comorbidities. The AKIGO criteria was used to identify the presence of AKI (?0.3mg/dL) in pre-to-postoperative change. We identified 1035 primary TKAs that met the inclusion and exclusion criteria (110 African American, 925 Caucasian). African American patients had significantly greater serum creatinine preoperatively (1.00 ± 0.26vs.0.90 ± 0.22, p<0.001) and a significantly greater increase postoperatively (0.10 vs. 0.03, p < 0.001). A significantly greater number of African American patients demonstrated changes consistent with AKI (12/110,10.9% vs. 47/925,5.1%, p=0.03). A significantly greater number of African American patients stayed in the hospital ?2 extra days specifically for renal issues (3/110, 2.7%vs.4/925, 0.4%, p = 0.03). Altered renal function was significantly more common in African American patients after primary TKA.

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Oral Presentation Session B

Abstract Title:	**Evaluation of Postnatal Growth and Caloric Intake in Relation to Intermittent Hypoxemia**
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Abstract: Background: Intermittent hypoxemia (IH) occurs invariably in preterm infants and may have cumulative effect on morbidities. Data from animal models suggest that IH impairs growth however no studies exist in preterm infants. Methods: Infants ?29wks gestational age (GA) were prospectively enrolled. Oxygen saturation (SpO2) was continuously monitored using high-resolution pulse oximeters. Weekly growth measures (Z-scores: weight, length, head circumference) and caloric intake were calculated. IH measures defined as: Primary, %time-SpO2<80: percent time spent with SpO2<80%/week; Secondary, IH-SpO2<80: Number of events/week with SpO2<80%. Correlations were calculated weekly. Model analysis for caloric intake was adjusted for GA and day of life. Results: 100 infants were included. Median GA was 26.3wks (IQR25.1-28.5); Birth weight 898g (IQR690-1095) and caloric intake 124kcal/kg/day (IQR66-124). There was no statistically significant correlation between IH and growth measures. However, there was a positive relationship between IH and caloric intake for both %time-SpO2<80 (Estimate 3.01, SE 0.39, p<0.0001) and IH- SpO2<80 (Estimate 0.054, SE 0.012, p<0.0001). I.e. for every additional 1% of time with SpO2<80, mean caloric intake increased by 3kcal/kg/d adjusting for GA and postnatal day of life (p<0.0001). Conclusion: Our results did not show an association between IH and growth in preterm infants. Interestingly, infants with IH were noted to have statistically significant higher caloric intake with more severe IH. We speculate that infants with increased IH did not show impaired growth because of close monitoring of growth parameters and subsequent nutrition adjustment during NICU stay.

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Oral Presentation Session B

Abstract Title:	**Regional Telehealth Network for the Management of Neonatal Abstinence Syndrome in Infants from Rural Areas of Kentucky**
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Abstract: Background: Given the rising prevalence neonatal abstinence syndrome (NAS) and the high costs associated with its care, there is a clear need to disseminate best-practices in the management of this patient population. As a major referral center and experts in the field, our Division of Neonatology is in position to establish relationships with regional sites to create uniform and evidence-based strategies for the management of NAS. Objectives: To implement a NAS care protocol in a regional consortium of hospitals. To determine the effectiveness of telehealth in the management of these patients at their community hospital. Methods: Establish a regional approach for NAS. [Months 1-6]. Identify physician (PI) and nurse champions at each participating nursery, compare current practices at each site and determine individual site length of stay. Develop a uniform treatment protocol based on evidence best practices and establish outcome measures. Determine outcome measure recording, documenting and report. Implement a uniform NAS protocol and multidisciplinary discussions. [Months 6-18] Weekly multidisciplinary videoconference between neonatologists, nurses, pharmacists and social worker from Kentucky Children's Hospital and the providers at the regional sites to discuss patient management and concerns. Implementation, compliance, outcomes measures and data collection will be discussed quarterly between PI's. Changes to the process or to the protocol will be proposed and implemented as needed. Data analysis before vs after implementation of the regional protocol. [Months 18-24] Expected results: This model of care will result in decrease length of stay as well as hospital charges, with an overall improvement in clinical outcomes.

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Oral Presentation Session B

Abstract Title:	**Voices of Hope: A Feasibility Study of Telephone Recovery Support**
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Abstract: Background: Substance use disorders (SUDs) are chronic disorders that are often managed with crisis stabilization or short-term treatment. To improve rates of sustained remission from SUD, there is a need for long-term recovery support. Telephone recovery support (TRS) is a promising model, consisting of weekly calls from volunteers to people in early recovery to offer support and connect participants with resources. The aim of this study was to conduct a program evaluation of the effectiveness of a TRS program in Central Kentucky to determine feasibility. Methods: Participants (n=60) were recruited for the program from halfway houses, a drug court program, a detention center, and a local clinic for mothers with perinatal opioid use disorder. For each call, data was recorded including participant status (e.g, experiencing psychosocial stressors, concerned about relapse) and call duration. Results: Participants are predominantly female (75%) and overwhelmingly white (97%). Since the program's inception in November 2017, volunteers have made 329 calls and successfully completed 125 (38%) of those calls. Of the completed calls, 72% of participants reporting being "okay," while 24% reported "life problems." Moreover, 4% of participants reported concerns about relapse. Conclusion: TRS holds promise as a resource to promote extensive recovery support. More research is needed to examine the program's impact.

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Poster Presentation #1

Abstract Title:	**CD36 is upregulated in primary and metastatic colorectal cancer patient derived xenographs; a possible resistance mechanism of FASN inhibition.**
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Abstract: Fatty Acid Translocase (CD36), a multifunctional glycoprotein has been shown to have an important role in fatty acid metabolism as a fatty acid receptor and transporter across the plasma membrane. It has been shown in oral carcinoma that increased amounts of CD36 expression correlate positively with increased oral carcinoma metastasis. Clinically, the presence of CD36+ metastasis initiating cells correlates with a poorer prognosis in glioblastoma and oral carcinoma. Fatty Acid Synthase (FASN), a critical enzyme involved in de novo lipogenesis, has been shown to be upregulated and associated with poorer prognosis in many cancers including colorectal cancer (CRC). The role of CD36 in CRC primary and metastatic tumors as well as it relation to de novo fatty acid synthesis is not fully understood. The purpose of our study was: (i) To determine the role of membrane associated CD36 in primary and metastatic CRC. (ii) To delineate the association of CD36 expression with FASN as a possible mode of CRC FASN inhibition resistance. METHODS. CD36 expression was measured, along with FASN expression via immunohistochemistry and Tissue Micro-Array (TMA) in matched normal colon and primary CRC tumor tissues from patients who were diagnosed with Stage I-IV CRC and who underwent surgery at the University of Kentucky Chandler Medical Center (n=57 normal and 56 tumor tissues). CD36 expression was also analyzed in matched normal colon mucosa, primary CRC tumor and metastatic CRC tumors (Liver [n=12] and lung metastasis [n=5]) from patients who had been diagnosed with Stage III-IV CRC and who underwent surgery at the University of Kentucky Chandler Medical Center. An APC/FASN/CRE intestinal knockdown mouse model as well as a FASN shRNA in vitro knockout model were used to analyze CD36 expression levels. Cell proliferation assays were performed using primary CRC cells from patient derived xenographs (PDXs) in combination with Sulfo-N-succinimidyl oleate (SSO), an irreversible inhibitor of CD36, and FASN inhibitor TVB-3664. CD36 expression levels in primary and metastatic PDX derived CRC cells were analyzed via western blot and immunofluorescence imaging. RESULTS. CD36 was found to be over expressed in CRC primary tumor tissue when compared to normal colon. Furthermore, CD36 exhibited a correlation with FASN expression in CRC primary tumor. Cell proliferation was significantly reduced when CD36 was inhibited by SSO and a further reduction in cell proliferation was observed when SSO treatment was combined with TVB-3664. Treatment of primary CRC cells with SSO displayed an induction in cell apoptotic markers such as cleaved capspase-3 and a decrease in the survival marker survivin. Western blot analysis of primary and metastatic CRC cells saw an upregulation of CD36 expression in the metastatic CRC primary cells. Additionally, in murine APC/FASN/CRE intestinal knockdown tissues as well as FASN shRNA knockout cells, an induction of CD36 expression was observed. Immunofluorescence imaging of primary CRC cells which were treated with TVB-3664 show an upregulation of membrane bound CD36. CONCLUSION. Our studies indicate that CD36 upregulation is associated with primary and metastatic CRC progression. Furthermore, inhibition of CD36 in primary CRC cells show a decrease in cell proliferation and survival. Importantly, CD36 was shown to be upregulated in primary CRC cells when FASN was inhibited or knocked down, indicating CD36 as a possible mode of resistance to FASN inhibition. Continuing studies of CD36 expression in primary and metastatic CRC may indicated further therapeutic targets for treatment of CRC patients which may display resistance to FASN inhibition.

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Abstracts

Poster Presentation #2

Abstract Title:	**Identifying Novel Therapeutics to Inhibit the Wnt Self-Renewal Pathway in Leukemia Stem Cells**
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Abstract: Although leukemia has a high cure rate, it is plagued by a high relapse rate and 15-20% of pediatric leukemia patients that go into remission will go on to have return of their disease. This relapse rate is likely due to a small population of cells known as leukemia stem cells (LSCs). Current efforts to study LSCs have faced serious limitations which have impeded our understanding of this population of cells. Prior work in our lab has established a zebrafish Myc-induced T-cell acute lymphoblastic leukemia (T-ALL) model that mimics the most aggressive and treatment resistant form of human T-ALL. Using this system, we were able to isolate single LSCs through a novel transplantation strategy. Analysis of growth rates at different limiting dilutions showed significant differences in the rate of self-renewal between different LSCs. Importantly, a subset of LSCs acquired increased self-renewal over time. We were able to generate a library of zebrafish T-ALL with very high self-renewal rates (about 1/10 cells is a LSC) that will be used to study LSC properties more efficiently. We analyzed these primary T-ALLs using RNAseq and single cell qPCR to compare expression profiles of the leukemias with low self-renewal rates to those with high self-renewal rates. This single cell qPCR showed a population of cells that expressed known self-renewal genes and had a very different gene expression profile than the rest of the cells in the population. This population was assumed to be LSCs and several novel genes were identified as markers of these LSCs. From this analysis, the Wnt pathway, more specifically ß-catenin, was identified as an important marker that was enriched in LSCs and not in the rest of the population of leukemia cells. Our collaborator at the University of Kentucky, Dr. Chunming Liu PhD, has designed a panel of 5 different families of Wnt inhibitor compounds which work at various points in the Wnt/B-catenin signaling pathway. We screened several of the Wnt inhibitor compounds in vivo using 6xTCF/LEF:GFP zebrafish which serve as Wnt pathway reporter fish. Several of the Wnt inhibitor compounds showed significantly decreased GFP expression after drug treatment, indicating inhibition of the Wnt pathway in vivo. In the future we plan to create a novel zebrafish model to mark LSCs. We will use 6xTCF/LEF:GFP;Rag2Myc:mCherry zebrafish as an in vivo model of LSCs. We then plan to use these zebrafish to screen our Wnt inhibitor drug compounds to see if they decrease LSC frequency, indicating inhibition of the LSC self-renewal pathway. We hypothesize that inhibitors of the Wnt pathway will inhibit self-renewal of LSCs and force them to differentiate into normal leukemia cells, representing a potential therapeutic strategy for targeting treatment-resistant LSCs.

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Abstracts

Poster Presentation #3

Abstract Title: **Neurotensin Increases AMPK in Estrogen-Dependent Breast Cancer Cells**

Author(s): J. Johnson, Department of Toxicology & Cancer Biology, U of Kentucky
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Abstract: Introduction. Neurotensin (NT) is a thirteen amino acid peptide mainly involved in regulating lipid metabolism and storage. NT can also act through its high-affinity receptor (NTR1) to stimulate the growth and progression of a variety of NTR1-positive cancers. However, very little is known about the underlying NT signaling pathways that stimulate breast cancer growth. The purpose of this study is to elucidate mechanisms by which NT affects breast cancer. Methods. MCF-7 (estrogen-dependent) and MDA-MB-231 (triple negative) are breast cancer cell lines that express NTR1. (i) To assess signaling pathways mediating the effects of NT, both cell lines were treated with NT (0 or 100 nM) in serum-free media for a variety of times; immunoblotting was performed for phosphorylated and total forms of AMP-activated protein kinase (AMPK) and its downstream effector acetyl CoA carboxylase (ACC). (ii) Proliferation and invasion assays were conducted in a variety of different ways. Results. (i) NT induced activation of AMPK and ACC in MCF-7 cells but not in MDA-MB-231 cells. (ii) These changes in AMPK were not linked to any changes in cellular proliferation or invasion. Conclusions. Our findings indicate that NT activates AMPK and its downstream effector in estrogen-dependent breast cancer cells. These effects were minimal in NTR1-expressing triple negative breast cancer cells, suggesting that the molecular classification of the tumor plays an important role in NT signaling. Further delineating the differential effects of NT in specific breast cancer phenotypes has the potential to identify novel therapeutic targets in the treatment of this disease.

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Poster Presentation #4

Abstract Title:	**Regulation of UV-Induced ?-defensin 3 (BD3) Expression in Human Keratinocytes and Physiological Consequences of BD3 on Melanocytic DNA Repair and UV Mutagenesis**
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Abstract: Melanoma has become increasingly prevalent over the past 30 years, largely fueled by increased exposure to UV through unprotected sunlight exposure and indoor artificial tanning. UV radiation causes DNA damage to keratinocytes in the epidermis of the skin. Melanocortin 1 receptor (MC1R) is a Gs-protein coupled melanocytic receptor that plays a critical role in the ability of keratinocytes and melanocytes to recover from UV damage. Research has recently indicated that MC1R can be inactivated by beta-defensin 3 (BD3). Our research focuses on the effects of UV exposure on BD3 expression in epidermal keratinocytes, as well as the physiological consequences of BD3 expression on melanocytic DNA repair and UV mutagenesis. We hypothesize that UV exposure will induce BD3 expression in epidermal keratinocytes and regulate melanocyte physiology through damage response pathways activated by UV. Human keratinocytes were exposed to 250 J/m2 of UVB for varying durations. ASIP, BD3, p21, p38, p53, and POMC mRNA expression was determined at 0, 4, 8, 12, 16, 20, 24, 48, and 72 hours following UV treatment. The data from five qPCR analyses of gene expression was recorded. Gene expression was found to be relatively inconsistent over the five analyses. Nonetheless, general trends were still noted. The overall trends can aid in the direction of future studies, in particular, the relationship between BD3 and p53 expression.

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Abstracts

Poster Presentation #5

Abstract Title:	**Divergence of cAMP Signaling Pathways Mediating Augmented Nucleotide Excision Repair and Pigment Induction in Melanocytes**
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Abstract: Loss-of-function melanocortin 1 receptor (MC1R) polymorphisms are common in UV-sensitive fair-skinned individuals and are associated with blunted cAMP second messenger signaling and higher lifetime risk of melanoma because of diminished ability of melanocytes to cope with UV damage. cAMP signaling positions melanocytes to resist UV injury by up-regulating synthesis of UV-blocking eumelanin pigment and by enhancing the repair of UV-induced DNA damage. cAMP enhances melanocyte nucleotide excision repair (NER), the genome maintenance pathway responsible for the removal of mutagenic UV photolesions, through cAMP-activated protein kinase (protein kinase A)-mediated phosphorylation of the ataxia telangiectasia mutated and Rad3 related (ATR) protein on the S435 residue. We investigated the interdependence of cAMP-mediated melanin upregulation and cAMP-enhanced DNA repair in primary human melanocytes and a melanoma cell line. We observed that the ATR-dependent molecular pathway linking cAMP signaling to the NER pathway is independent of MITF activation. Similarly, cAMP-mediated up-regulation of pigment synthesis is independent of ATR, suggesting that the key molecular events driving MC1R-mediated enhancement of genome maintenance (e.g. PKA-mediated phosphorylation of ATR) and MC1R-induced pigment induction (e.g. MITF activation) are distinct.

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Poster Presentation #6

Abstract Title:	**Using Protein-Protein Interaction Networks to Generate Hypotheses for Gene Function and Derive Process-Specific Pathways**
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Abstract: We have built a comprehensive Protein-Protein Interaction (PPI) network for human by aggregating and integrating PPI and other interaction data from several publicly available resources. We are able to filter this custom network based on a variety of criteria including gene expression, mutational patterns, phenotype, disease, and functional annotation, enabling a wide range of interaction network analyses. Moreover, we can overlay a variety of annotations onto the network. We can use these analyses to generate functional hypotheses for genes with limited functional information and to derive a pathway/module for a group of related genes-products involved in a common process. We are also integrating this custom interaction network and related tools with other tools being developed in our lab, including: i) GOcats, which creates custom categories for sets of Gene Ontology annotations, and ii) categoryCompare, which can utilize arbitrary annotations generated from knowledgebases, GOcats, and this custom interaction network to perform multiway annotation enrichment analyses. With our methods, we demonstrate a variety of hypothesis generation and pathway derivation use-cases. In particular, we have generated functional hypotheses for the under-studied gene PCMTD1 within the context of lung squamous cell carcinoma utilizing both mutational patterns derived from whole exome sequencing data and PPIs. Furthermore, we have derived cancer-specific pathways for both PCMTD1 and IDH1 utilizing a variety of PPI, functional annotation information, and mutational patterns [1].

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Poster Presentation #7

Abstract Title:	**Lower Serum Albumin is associated with poorer Outcomes in Head and Neck Cancer Patients Receiving ChemoRadiotherapy**
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Abstract: Background: Locally advanced head and neck cancers can profoundly impact patients' nutritional status at presentation. Current literature primarily associates low albumin (a marker of nutrition) with poorer outcomes in surgically treated head and neck cancer patients. We hypothesized that hypoalbuminemia is associated with poorer outcomes in patients with advanced head and neck cancers receiving chemoradiation. Methods: 114 patients with stage III and IV head and neck cancer who received chemoradiation from 2007-2015 at University of Kentucky were analyzed. IRB approval was obtained prior to the study. Medical records were used to collect pre-treatment albumin, RECIST criteria, and control rates. Relative risks of overall recurrence and of metastasis at 6 months, 2 years, and 5 years were calculated for hypoalbuminemia (<3.5 mg/dL) and eualbuminemia (?3.5 mg/dL) cohorts. Results: 88 patients with eualbuminemia (Median age 57, 83.91% male. Stage:14.8% III, 62.5% IVA, and 5.7% IVB) and 26 hypoalbuminemic patients (Median age 58, 73.08% male. Stage: 7.7% III, 65.38 % IVA, and 15.38% IVB) were compared. Hypoalbuminemia was associated with significantly ($p < 0.05$) lower metastasis free survival at 6 months (Risk 38% vs 9%, RR (95% CI) of metastasis/death= 4.23 (1.86-9.61)) compared to eualbuminemic patients. Hypoalbuminemia was associated with increased overall recurrence (Risk 56% vs 30%, RR (95% CI) = 1.90 (1.18-3.05)). Conclusion: Low pre-treatment albumin in patients with advanced head and neck cancer is associated with poorer outcomes following chemoradiation. Aggressive nutritional resuscitation should be attempted prior to chemoradiation in patients with advanced Stage IV B head and neck cancer.

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Abstracts

Poster Presentation #8

Abstract Title:	**The Geographic Management of Cancer Health Disparities Program (GMaP): Leveraging Pilot Projects to Increase Successful Applications for National Cancer Institute CURE Program Funding for Underrepresented Cancer and Health Disparities Researchers**
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Abstract: Introduction A major goal of GMaP is to facilitate the career development of underrepresented cancer researchers by promoting and increasing applications to the NCI CURE Program. The CURE Program provides funded training opportunities to students at all career levels to ensure a continuum of career development opportunities in cancer health disparities research. One way GMaP is working to help trainees in their applications is through a Pilot Project Award Program. Procedures GMaP has developed a pilot project application and review process. Pilot opportunities are promoted through the GMaP website and listserv. Applications are reviewed internally using NIH review criteria. Applicants must demonstrate their plans for applying for a CURE Program award in the future. Pilot awards are up to $10,000 in total cost funding for one year. Project progress is monitored by GMaP staff and awardees are required to present results to GMaP investigators. GMaP offers assistance and tracks future applications for NCI funding. Results The following pilot projects will be presented, including a synopsis of the design, current results and subsequent NIH applications submitted:Supporting Advance Care Planning in African Americans; Effect of Emotion on Prostate Cancer Treatment Decision Making; Effects of Obesity on Promotion of Breast Cancer by Amplifying the LPA/ATX Signalling Nexus; PAP Screening in sub-Saharan Immigrant Women; Development of a Molecular Panel to Detect Cervical Intraepithelial Neoplasia; Meal Timing and Its' Effect on Inflammation and Adverse Health Outcomes in African American Women

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Abstracts

Poster Presentation #9

Abstract Title:	**Biodegradable Polymer Enhance Mesenchymal Stem Cells Retention After Transplantation**
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Abstract: Mesenchymal stem cells (MSCs) have generated much interest as a source of cellular therapy owing to their self-renewable, multi-lineage differentiation, and immunomodulatory potential. However, MSC mediated therapeutic benefits are strongly correlated with the number of cells injected. As such, the engraftment efficiency of MSCs at transplantation sites critically influence their success. This is particularly concerning for cardiac tissues given the mechanical contractions and hydrostatic pressures that drive heart function. In fact, less than 5% of transplanted cells are retained in heart tissues within 24 hours post injection. To enhance MSC based cellular therapy, we isolate, expand and characterize murine GFP+ MSCs from total bone marrow based on their plastic adherence. Isolated cells are expanded in vitro with serial passages to a homogeneous MSC population based on characteristic surface markers. In a collaborative effort, we have developed a biodegradable 100 nM gelatin methacrylate (gelMA) cell surface coating polymer that does not compromise MSC survival and metabolic activity. To evaluate the engraftment efficiency of gelMA coated MSCs in vivo, we injected coated and uncoated GFP+ MSCs into a non-GFP mouse model post myocardial infarction, induced by left anterior descending artery ligation. The retention of GFP+ cells was evaluated by flow cytometry and immunohistochemistry. Our preliminary data demonstrated a higher percentage of GFP+ cells in mice treated with coated cells compared with uncoated cells. Our data provide first evidence that biodegradable coating can enhance the retention of transplanted MSCs and provide the basis for more successful regenerative therapies.

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Poster Presentation #10

Abstract Title:	**Computation of Baroreflex Sensitivity During Listening to Music Using two methods: Time Domain Sequences and Frequency Domain Transfer Functions**
Author(s):	D. Biswal, M. J. Mollakazemi, S. Thyagarajan, J. Evans, A. Patwardhan

Abstract: Listening to music has been known to affect autonomic function of cardiovascular regulation. Baroeflex is a feedback control loop that uses rate changes of the heart in order to regulate beat by beat changes in blood pressure (BP). Baroreflex sensitivity (BRS) provides a quantitative measure of functioning of baroreflex. Although interventions such as vasoactive drugs, which produce reliable and large changes in BP are used to assess BRS, in situations such as listening to music where subtle changes are expected non-invasive methods are advantageous. In this study, we used two non-invasive approaches to compute measures BRS, a time domain sequence approach and frequency domain transfer functions. Subjects listened to slow and fast tempo songs during the study. Electrocardiogram (ECG) and non-invasive continuous BP were recorded in 14 subjects (7 males and females). From these signals, either beat by beat or equi-sampled in time RR intervals and systolic BP (SBP) were computed. BRS was then estimated using RR and SBP. Our results show that the sequence method consistently provided higher values of BRS than the transfer function method (up to two fold). The two measures were reasonably well correlated (R>0.84) during control and the slow song, but not during the fast song. The BRS was lower (~20%) than control when listening to fast songs ($p < 0.005$). These results show the effects of listening to songs on BRS changes, but also show that the two methods to estimate BRS, although reasonably correlated, do not always provide similar estimates of BRS.

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Poster Presentation #11

Abstract Title:	**Inducible Deletion of Adipocyte Prorenin Receptor reverses Obesity-related Hypertension in Male Mice**
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Abstract: Obesity contributes to approximately 2.5 million deaths every year and is associated with life threatening conditions including hypertension. This study aimed to investigate whether the deletion of adipose prorenin receptor (PRR) in obese mice reversed obesity-related hypertension. Male mice expressing an inducible adipocyte-specific Cre under the control of the adiponectin promotor were bred to PRR floxed mice female mice to generate inducible adipose-PRR KO male mice (ERT). Littermate PRR floxed male mice were used as controls. After 18 weeks of high fat feeding, ERT and control male mice (n=11-13 mice/group) were injected with tamoxifen. The inducible deletion of adipose-PRR significantly decreased body weight and white adipose tissues mass (visceral fat: Control, 3.17 ± 0.18 g; ERT, 2.05 ± 0.22g). To understand the mechanism involved in the reduction of white adipose tissue, the expression of genes involved in adipogenesis were examined. CEBP?, PPAR? and FABP4 genes expression were significantly decreased in epididymal fat of ERT mice compared to control. Metabolic examination of energy homeostasis depicted a significant increase of energy expenditure in ERT mice. Brown adipose mass was significantly increased in ERT mice. The systolic blood pressure was significantly reduced in ERT male mice after tamoxifen injection compared to control mice (Control, -2.5 mmHg; ERT, -8.87 mmHg). Adipose, liver and circulating components of the renin angiotensinogen system were not changed in ERT mice. Our results highlight a new signaling pathway involving PRR in adipogenesis, energy metabolism and blood pressure regulation. PRR could represent a new therapeutic target for obesity-related hypertension.

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Poster Presentation #12

Abstract Title:	**Anti-apolipoprotein A-I Antibody Profile Correlates With Cardiovascular Disease Outcomes**
Author(s):	D. Henson, Department of Pharmaceutical Sciences, U of Kentucky A. S. Tahhan, Division of Cardiology Emory Clinical Cardiovascular Research Institute A. A. Quyyumi, Division of Cardiology Emory Clinical Cardiovascular Research Institute V. Venditto, Department of Pharmaceutical Sciences, U of Kentucky

Abstract: Apolipoprotein A-I (ApoA-I) is a target of IgG autoantibody induction in patients, but the role of these antibodies has not been fully elucidated. Previous research has characterized anti-ApoA-I IgG antibodies targeting delipidated ApoA-I as a biomarker of cardiovascular progression, but only a moderate association was observed. We hypothesize that free anti-ApoA-I IgG is a single component of the anti-ApoA-I response and characterization of anti-ApoA-I antibody profiles will be more predictive of adverse cardiovascular outcomes. Given the relative concentrations of ApoA-I and anti-ApoA-I antibodies, we examined sera samples from 375 patients with coronary artery disease (CAD) to quantify soluble ApoA-I/IgG immune complexes (ICs). We found a range of ApoA-I/IgG IC concentrations in patients, irrespective of free anti-ApoA-I antibodies. While free antibodies failed to predict outcomes in this CAD cohort, a median Cox regression analysis over 6 years of follow-up determined a hazard ratio of 1.5 (95% CI: 1.03-2.18, p=0.03) for patients with below median ApoA-I/IgG ICs levels after adjusting for 11 traditional cardiovascular risk factors. In comparison, a cohort of healthy subjects exhibited significantly higher ApoA-I/IgG ICs. Pearson correlation analysis between ApoA-I/IgG ICs in the 375 patients with CAD and 25 patient characteristics found that only hypertension showed a significant association with ApoA-I/IgG ICs (r=-0.154, p=0.003). In addition, no significant relationship between ApoA-I/IgG ICs and total ApoA-I concentration (r=-0.0601, p=0.51) or total IgG concentration (r=0.134, p=0.137) was observed. Identification and ongoing characterization of ApoA-I/IgG ICs has the potential to guide clinical diagnosis and intervention strategies in patients with atherosclerotic cardiovascular disease.

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Poster Presentation #13

Abstract Title:	**Young adult mice exposed to postnatal neglect display downregulation of transcription factors in visceral white adipose tissue**
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Abstract: Exposure to early life stress or adverse childhood experiences is associated with a greater BMI and cardio-metabolic disease risk. We have previously shown that maternal separation and early weaning (MSEW), a model of early life stress and neglect, exacerbates adipose tissue expansion and metabolic dysfunction during obesity-induced hypertension in adult female MSEW mice compared with males. Thus, the goal of this study was to determine whether there are sex-specific changes in fat mass and glucose homeostasis in juvenile and young adult male and female mice exposed to MSEW. We also investigated the status of adipose tissue transcription factors. MSEW was performed by separating the pups from the mother for periods of 4 to 8 hour during postnatal days 2-16. Mice were weaned at postnatal day 17 (P17). Control mice remained undisturbed in the home cage at all times and were weaned P21. We used 7 control and 8 MSEW litters. All observations were averaged within litters by sex, and analysis was performed with litters as experimental units. Body weight (BW) were similar between male and female control and MSEW weanlings at P17, P19, P21. However, male and female MSEW mice showed increased fat mass measured by EcoMRI. At P60, one subset of littermates was placed on a low fat diet (LF, 10% kcal from fat) for 1 week. After 1 week, only female MSEW mice showed increased fat mass. The other subset of littermates was placed 1 week on a high fat diet (HF, 60% kcal from fat). MSEW increased BW and fat mass in both male and female HF-fed mice. Six-hour fasting glucose was higher in mice exposed to MSEW regardless sex or diet, although the oral glucose tolerance test was not different between groups. Further, gWAT was isolated in mice after 1 week of HF (n=4 each group), and mRNA was isolated for nanoString analysis of transcription factors (nanoString Technologies, Inc, Seattle, WA). We found that 1 week of HF significantly downregulated: Foxo1 (-1.24±0.07 fold), Sirt1 (-1.51±0.24 fold), Stat5a (-1.53±0.16 fold) and Foxp2 (-3.02±0.96 fold) compared with controls ($p<0.05$). Overall, MSEW does not affect BW but increases fat mass during postnatal life. Our study shows that, later in life, MSEW-induced increases in fat mass does not require HF in adult female mice. Downregulation of transcription factors such as Foxp2 could be linked to exacerbated obesity as reported in obese children.

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Abstracts

Poster Presentation #14

Abstract Title:	**Early Signatures of Bleeding and Mortality in Patients on Left Ventricular Assist Device Support: Novel Methods for Personalized Risk-Stratification**
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Abstract: Background: LVAD use is limited by GI bleeding, thromboembolism, and mortality. At present, little data is available to identify at-risk patients and guide clinical management. Our study aimed to determine whether early analysis of routine laboratory data, platelet activity, and thromboinflammatory biomarkers following implantation reveals: (1) pathophysiologic responses to LVAD hemodynamics and (2) trends that predict personalized risks of one-year adverse outcomes. Methods: We performed a prospective observational study with 64 participants who underwent LVAD implantation [HeartMate II (n= 49); HeartWare (n=15)] between March 2014 and 2016. Blood samples were collected at: baseline; post-op days 0, 1, 3, and 6; and during a follow-up visit. Platelet activity was analyzed by impedance aggregometry. Serum biomarkers were profiled by MAGPIX multiplex reader. Demographics, clinical characteristics, and laboratory data were collected. Results: At one year, GI bleeding occurred in 20% (n=13); multiple GI bleeding in 14% (n=9); hemorrhagic stroke in 9% (n=6); ischemic stroke in 11% (n=7); pump thrombosis in 13% (n=8). Early sustained thrombocytopenia ($p<0.001$) and increased mean platelet volume (MPV) ($p<0.001$) were associated with one-year GI bleeding. MPV also strongly predicted one-year mortality. Platelet activity declined following implantation and predicted one-year GI bleeding at early ($p=0.047$) and follow-up time points ($p=0.005$). Thromboinflammatory biomarker sCD40L strongly predicted one-year GI bleeding at baseline ($p < 0.001$) and the first week ($p< 0.010$). Conclusions: Biological responses to LVAD implantation manifest in routine laboratory data, platelet activity, and thromboinflamatory biomarkers. Early trends in these responses may serve as novel signatures of GI bleeding or thromboembolism.

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Abstracts

Poster Presentation #15

Abstract Title:	**Case Series: Improvement in Heart Failure Post LVAD - Is It a Long Term Disease Reversal or a Temporary Remission ?**
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Abstract: (VADs) Ventricular Assist Devices are offered to those HF(Heart Failure) patients who do not respond to the optimal medical management and cardiac resynchronization therapy and require heart transplant. VADs are used as a bridge to transplant or as a destination therapy but recent works explore the possibility of VADs use for potential recovery of the failing heart. One of them being a pivotal study by Emma Birks in 2011 which showed reversal of HF in a younger population after VAD explant who had been managed with LVADs and aggressive pharmacological therapy (7). Patients on VADs for a longer time have shown improvement in the hemodynamics of left ventricle as well as molecular and structural changes in the myocardium (5). But is this structural reverse remodeling after being unloaded with VADs (1) synonymous for myocardial recovery? In comparison to Drakos et al.(12), who found a 35% increase in capillary density with VAD unloading, Farris et al found no difference in capillary density and cardiac fibrosis (9). Also, Gupta et al used radio tracer uptake to study intrinsic cardiac structure and did not find any significant changes with VAD unloading the failing heart (11). Therefore, it seems complete normalization of functions of a failing heart may not be possible with VAD unloading and so " heart failure remission " may be an appropriate term instead of recovery as pointed out by The Editorial (10). In Support of this we present to you a total of 3 cases that showed recovery of functionality of heart (evaluated by Echo) after VAD placement but eventually deteriorated after VAD explant ranging within 4 years. Conclusion: Based on our experience with the cases above and the recent studies that have been done, recovering physiological parameters of heart with unloading may not essentially translate into " myocardial recovery " and indicate " remission " of the disease. To know if this is a complete final recovery or perhaps a temporary remission of HF needs to be addressed with large patient studies with long term f/u of patients Post VAD explant.

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Abstracts

Poster Presentation #16

Abstract Title:	**Circulating levels of Per- and Poly- fluro alkyl substances in subjects undergoing behavioral/lifestyle based interventions for cardiovascular disease risk reduction.**
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Abstract: Individuals living in Appalachia and in particular eastern Kentucky have far higher risk of cardiovascular diseases than the general population. Cardiovascular disease risk is largely determined by genetic and behavioral factors (for example poor diet and smoking). Substantial evidence also associates involuntary exposure to environmental agents, for example air pollution and environmental chemicals in foods and drinking water with risk of cardiovascular and metabolic diseases. Per- and poly- fluoroalkyl substances (PFAS) are widely detected in humans and the environment. Although the mechanisms involved are presently unclear, several epidemiological studies have identified a positive association between circulating levels of certain PFAS (notably perfluorooctanoic acid) and low density lipoprotein associated cholesterol which is a well-established risk factor for atherosclerotic coronary artery disease. Individuals living in and around the Ohio River Valley exhibit higher levels of exposure to these chemicals than the general population, possibly because of increased manufacturing and discharge in the region. We have established highly sensitive stable isotope dilution HPLC coupled electrospray ionization tandem mass spectrometry methods for quantitation of a series of PFAS in human plasma and serum. We will report on studies using these methods to measure levels of these substances in archived plasma samples from subjects living in Eastern Kentucky who were enrolled in a randomized clinical trial to test the efficacy of a lifestyle/behavioral modification regimen on cardiovascular disease risk factors measured at 4 and 12 months after initiation of the intervention.

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Abstracts

Poster Presentation #17

Abstract Title:	**Characterizing Unique Protein-protein Interactions in Sterol Biosynthetic Enzymes for the Control of Fungal Pathogens**
Author(s):	K.B. Linscott, Department of Molecular and Cellular Biochemistry, College of Medicine, U of Kentucky J. Chappell, Departments of Molecular and Cellular Biochemistry and Pharmaceutical Sciences, U of Kentucky

Abstract: Invasive fungal infections are a significant cause of patient morbidity and mortality, indicating a need for the identification of new therapeutic targets. Squalene synthase is the first committed step in sterol biosynthesis, and while this enzyme plays a critical role in cell growth, the protein architecture is shared among eukaryotes and so is resistant to the design of fungal-specific growth inhibitors. It has been shown that there is a unique component of the fungal carboxy-terminal domain which allows the fungal squalene synthase, not the enzyme from plants or animals, to complement a knockout mutation in yeast. We hypothesize that there is a fungal-specific motif within this domain involved in regulation of the sterol pathway that can be mimicked for the development of an antifungal therapeutic. To identify this motif, we used the yeast Saccharomyces cerevisiae with a squalene synthase knockout mutation and expressed chimeric squalene synthases originating from multiple kingdoms of life. In contrast to previous observations, all enzymes tested were able to partially complement the knockout mutation when the genes were weakly expressed. Induction of non-fungal squalene synthases could not complement the yeast mutation and led to the accumulation of carboxy-sterol intermediates. These results suggest that the motif is involved in mediating an interaction between squalene synthase and the downstream C4-decarboxylase. Restoration of the complete complementation phenotype was mapped to a kingdom-specific 26-amino acid hinge motif, and over-expression of the C-terminal domain containing this hinge motif from a fungal squalene synthase led to growth inhibition of wild-type yeast.

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Abstracts

Poster Presentation #18

Abstract Title:	**Leukemia Inhibitory Factor Differentially Modulates the Post-Stroke Immune Response in Aged Male and Female Rats**
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Abstract: Objective: To determine whether the anti-inflammatory effects of leukemia inhibitory factor (LIF) are altered in aged male and female rats. Methods: Focal ischemia was induced in 3 month old male and 18 month old male/female Sprague-Dawley using the middle cerebral artery occlusion (MCAO) procedure. Animals were treated with PBS or LIF at 6, 24, and 48 h after MCAO (125 ?g/kg). Infarct volume in aged animals was quantified with T2-weighted MRI. Functional motor skills were assessed immediately prior to euthanization at 72 h post-MCAO. Bone marrow-derived macrophages (BMDMs) were cultured and treated with PBS or LIF prior to induction of a pro-inflammatory phenotype (M1). Results: At 72 h, there was a trend towards decreased infarct volume in aged female LIF-treated rats compared to female PBS-treated rats. LIF promoted functional recovery as measured by three out of four motor skill tests in aged females but not aged males. Normalized CD11b levels were significantly in LIF-treated young males compared to PBS-treated young males. LIF increased spleen size and splenic CD11b levels compared to PBS-treated females. LIF significantly decreased IL-12 p40, and prevented the upregulation of IP-10 after MCAO in young male rats. In aged female rats, LIF treatment significantly decreased IFN? and IP-10 levels in the spleen compared to PBS-treated rats. At 24 h after induction of an M1 phenotype, LIF treatment significantly reduced IL-12 release and significantly increased IL-10 release among BMDMs. Conclusions: LIF promotes anti-inflammatory signaling in the splenocytes of young males and aged female rats, but not aged males.

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Abstracts

Poster Presentation #19

Abstract Title:	**Educational Exposure to Transgender Patient Care in Otolaryngology Training**
Author(s):	V. Rashidi, College of Medicine, U of Kentucky B. Massenburg, Division of Plastic and Reconstructive Surgery, U of Washington School of Medicine S.D. Morrison, Division of Plastic and Reconstructive Surgery, U of Washington School of Medicine

Abstract: Objective: Gender dysphoria is estimated to occur in over one million people in the United States. With decreasing stigma regarding the transgender population, it is likely more patients will seek medical and surgical gender affirmation as parts of their treatment. However, otolaryngologists may lack training in gender-affirming surgery. This study aims to determine the current state of transgender-related education in United States otolaryngology training programs and to evaluate trainee perceptions regarding the importance of such training. Methods: A cross-sectional survey was performed among United States otolaryngology training programs. A representative sample of 22 training programs divided within four U.S. Census regions completed a cross-sectional nine-question survey between March and May 2017. Respondents were queried regarding demographics, transgender curricular exposure (didactic and/or clinical), and perceived importance of training in transgender patient care. Results: A total of 285 trainees responded (69.3% response rate). Thirty percent of respondents reported education on or direct exposure to transgender care during residency. Among those with experiences in gender-affirming surgery, more than half were exposed to facial (masculinization or feminization) or pitch alteration surgery. Overall, the majority of respondents believed training in gender-affirming surgery is somewhat important and 63.2% supported incorporation of transgender patient care in existing subspecialty fellowship training. Conclusion: Less than one third of otolaryngology trainees are exposed to transgender patient care. The majority of trainees endorsed the importance of residency and subspecialty fellowship training in gender-affirming surgery. To better serve the transgender population, formal didactics on gender-affirming surgery should be offered.

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Abstracts

Poster Presentation #20

Abstract Title:	**Examining self-rated patients' knowledge about acute kidney injury (AKI) in patients followed in a dedicated AKI clinic**
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Abstract: Background: Acute kidney injury (AKI) survivors are at high risk of adverse outcomes. There are few clinics dedicated to improving the care of these patients. Specialized post-discharge nephrology care may improve AKI literacy and prevent renal and non-renal complications. Methods: We conducted a quasi-experimental qualitative study of 104 AKI survivors not on renal replacement therapy. Patients self-rated their level of knowledge about the AKI diagnosis and the level of severity of their AKI at two time-points: pre- and post-their first AKI clinic encounter. AKI was defined by KDIGO criteria. Patients' ratings (scale: 1 lowest to 5 highest) were compared by KDIGO stages. Mixed-model ANOVAs and multivariable logistic regression were utilized. Results: Mean (SD) age was 55 (13.8) years, 50% were males and 88.4% whites. AKI KDIGO severity was as follows: stage 1 or 2 18.2%; stage 3 48%; and stage 3-RRT 33.7%. Patients' self-ratings of their knowledge about AKI significantly increased after the first clinic encounter [mean (SD): 1.9 (1.2) to 3.9 (0.9), p=0.001] and when stratified by each KDIGO stage (p<0.001 for all groups). This improvement was independent of age, gender, KDIGO stage, and poverty metrics, suggesting that the education provided in the AKI Clinic was the main driver of this improvement. Conclusions: Post-discharge specialized nephrology care in a dedicated AKI Clinic increased patients' self-perceived knowledge about AKI. Further examination of AKI literacy in AKI Survivors and most importantly, the impact of AKI literacy on post-AKI outcomes are needed.

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Abstracts

Poster Presentation #21

Abstract Title:	**Improving Patient and Work Flow in the UK Internal Medicine Clinic**
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Abstract: The purpose of this quality improvement project was to improve workflow and decrease waste within the Internal Medicine Clinic at UK Healthcare. Initially through extensive investigation it was found that allowing clinicians open rooming within the clinic would prove the most beneficial, but in accordance to time, efficiency and money the process chosen to improve upon was a standardized of protocol for rooming patients. The American Medical Association's protocol was adopted and changed slightly to fit the clinic's needs. Through what is a called a small cycle of change, this protocol was adopted by a clinician and CST team over a 3-week period. Although there are many constraints in this study, mainly time, the results of this small cycle of change were found to be positive. Care was found to be more safe, timely, effective, efficient and patient centered.

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Poster Presentation #22

Abstract Title:	**Epithelial-Specific P85? KO Enhances Crypt Resilience to Radiation Injury**
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Abstract: While high-dose radiation remains an effective treatment for aggressive cancers, it also exerts stress on physiologically high cycling cells, including intestinal epithelial cells (IEC), where it causes significant toxicity (diarrhea, bleeding, etc). Here we examine the role of PI3-Kinase (PI3K) signaling in promoting epithelial repair after radiation injury. To interrogate the role of IEC PI3K in radiation injury, we utilized VillinCre-p85fl//fl (p85KO) and VillinCre-p85+/+ subjected to high dose (12Gy) radiation. IEC Western blot (WB) data of p85KO mice at baseline revealed a complete ablation of p85?, with subsequent increases in p-AktSer473 along with p-PTEN, p-GSK3?Ser9, as well as anti-apoptotic protein survivin compared to WT controls, suggesting a deregulation of PI3K machinery. RT-PCR studies performed at baseline revealed increases in TA-enriched Wnt target genes, Axin2 (56%) and c-myc (39%) and reserve intestinal stem cell (ISC) markers HopX (33%), and Bmi1 (20%), at the expense of the active cycling Lgr5+ stem cells (-25%). Histopathologic sections highlight a distinct shift in the zone of proliferation with more than a 2-fold increase in BrdU+ cells at the reserve stem cell position 4 compared to controls. Following lethal radiation dosage, p85KO mice exhibited a 20% increase in survival as compared to wildtype (WT) littermates along with increased crypt survival (29% change). In p85KO mice, radiation induced lower levels of PUMA and cleaved caspase 3 compared to WT controls. Our data suggest PI3K signaling enhances recovery from radiation injury through expansion of reserve ISC populations capable of re-creating proliferative Lgr5+ ISC and accelerating crypt recovery.

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Poster Presentation #23

Abstract Title:	**Mitochondrial Impairment and Mucosal Healing in IBD**
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Abstract: Mucosal healing during inflammatory bowel disease (IBD) is regulated by intestinal epithelial cell (IEC) responses to cytokines, growth factors, and hypoxia. In this study we examined the connection between mitochondrial activity and ulcer healing through epithelial-to-mesenchymal transition (EMT). Analysis of IEC from human biopsies showed that active IBD reduces mitochondrial complex I, III, IV and V mRNA and protein by 70% and mtDNA copy number by 60%. There is a significant increase in mitochondrial transcription factor A (TFAM) levels, along with mitophagy/autophagy proteins p62, NIX, PINK1, LC3 and IRGM1. To assess the impact of mitochondrial depletion on ulcer healing, mice lacking TFAM in IEC were utilized for colitis studies. Cells deficient in TFAM have reduced mtDNA copy number and impaired oxidative phosphorylation. TFAM KO colons exhibit more extensive ulceration and elevated disease activity scores relative to wild-type (WT) mice. Interestingly, colitis increased the proportion of WT "escapers" in TFAM KO mice, suggesting that intact mitochondrial function provides a selective advantage during ulcer healing that is not present at baseline. To assess the connection between mitochondrial respiration and epithelial restitution, we analyzed human biopsies for markers of EMT. In IBD patients, active disease induced expression of EMT markers snail, slug, twist, and vimentin, and reciprocal regulation of E-cadherin and N-cadherin. Immunohistochemistry of biopsies revealed expression of EMT markers in ulcer margin crypts and newly formed epithelial monolayers. We speculate that glycolysis is sufficient for IEC homeostasis, but that mitochondrial respiration is needed for EMT and IEC migration during ulcer healing.

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Poster Presentation #24

Abstract Title:	**Advances in Gene Ontology Utilization Improve Statistical Power of Annotation Enrichment**
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Abstract: Ontologies are used extensively in scientific knowledgebases to organize the wealth of available biological information. However, gene-annotation enrichment queries utilizing these resources can provide thousands of results with weak statistical significance that are difficult to interpret without manually sorting into higher-order categories. Critically, some ontology relations are directionally opposite with respect to scope, hampering categorization and necessitating their omission lest erroneous term mappings occur. This omission leads to at least a 6% reduction in retrievable relational information in the Gene Ontology (GO), yet including these terms results in over 31% (325,180 out of 1,036,141) of term mappings being erroneous with respect to categorization when current tools are used on existing relations.To address these issues, we present GOcats, a novel tool that organizes GO into subgraphs representing user-defined concepts, while ensuring that all appropriate relations are congruent with respect to scoping semantics. Specifically, GOcats inverts the problematic has_part relationship directionality to represent the logic of part_of_some in order to maintain congruency of scoping semantics, eliminating the need for excluding problematic relations in the context of enrichment. We have integrated GOcats with CategoryCompare to enable GOcats-enhanced annotation enrichment analysis. Using CategoryCompare with two versions of the GO graph, one with has_part edges omitted and one with GOcats' part_of_some edges, we performed enrichment on an Affymetrix microarray dataset of ER+ breast cancer cells with and without estrogen exposure. We observed significant improvements (two-sided binomial test p-value=3.7265E-25) in 182 of 217 significantly enriched GO terms when GOcats was used with part_of_some edges.

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Abstracts

Poster Presentation #25

Abstract Title:	**Small Molecule Isotope Resolved Formula Enumerator (SMIRFE): a tool for truly untargeted metabolomics analysis of metabolites represented in Fourier transform mass spectra**
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Abstract: Fourier-transform mass-spectrometry (FTMS) is often utilized in the detection of small molecules derived from biological samples. What is directly detected in the FTMS spectra are peaks for related sets of isotopologues or molecules that differ only in their isotopic composition for various adducted and charged species corresponding to specific molecules present in a biological sample or introduced by contamination. The sheer complexity of what is detected along with a variety of analytically-introduced variance, error, and artifacts have hindered the systematic analysis of the complex patterns of detected peaks with respect to isotopic content. We have implemented a novel algorithm SMIRFE that detects small biomolecules less than 2000 daltons at a desired statistical confidence and determines their specific elemental molecular formula (EMF) using detected cliques of related isotopologue peaks with compatible isotope-resolved molecular formulae (IMFs). The current implementation efficiently searches a roughly 200 quintillion (2x1020) IMF space for each peak's m/z, but larger IMF spaces are searchable. We validated the assignment performance using verified assignments from a FTMS spectrum of a biological sample treated with ethylchloroformate, a chemoselection agent. SMIRFE provides both high accuracy for untargeted assignment for verified metabolite cliques and unambiguous IMF assignment for over half of the detected peaks in analyzed peak lists. Furthermore, SMIRFE provides E-value estimates of assignment accuracy, which no other available metabolite assignment tool provides. Also, SMIRFE has none of the limitations of current methods that can only detect known metabolites in a database. Thus, this new method enables a truly untargeted metabolomics analysis.

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Abstracts

Poster Presentation #26

Abstract Title:	**Defining an Electronic Phenotype for Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis in an Electronic Health Record Paired with a DNA BioBank Facilitates Genetic Discovery**
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Abstract: Stevens-Johnson Syndrome/Toxic epidermal necrolysis (SJS/TEN) is the most severe T-cell mediated adverse drug reaction (ADR), associated with mortalities of 30% or higher and significant short and long-term complications. Strong class I HLA-B associations have been defined for SJS/TEN for several drugs, which offer a potential preventive screening strategy, but associations for most drugs and populations remain undefined. Vanderbilt University Medical Center's (VUMC's) DNA repository BioVU, paired with the Synthetic Derivative (SD), its de-identified electronic health record system, offers a platform for developing a robust electronic phenotype for SJS/TEN to facilitate the discovery of genetic associations with this condition. Using ICD9/10 codes, keywords, and time restraints, we developed an electronic phenotype in the SD that identified patients who had been treated for SJS/TEN at VUMC. This electronic phenotype was extremely sensitive, identifying 35/36 (97%) of Bactrim-induced and 25/28 (89%) of Phenytoin-induced SJS/TEN cases in the SD. Of the cases we identified, 25 had DNA samples in BioVU available for genotyping. We genotyped the HLA-B genes of these cases and found that their alleles clustered around alleles with known shared peptide-binding specificities, namely the superfamilies of B7 and B44. Our methodology here provides a framework for developing electronic phenotypes of SJS/TEN that can be validated across other large electronic health record databases.

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Center for Clinical and Translational Science

Abstracts

Poster Presentation #27

Abstract Title:	**Interactive Clinical Event Pattern Mining and Visualization Using Insurance Claims Data**
Author(s):	S. Kim, Division of Biomedical Informatics, U of Kentucky A. Lenert, Division of Rheumatology, U of Kentucky Z. Piao, Division of Biomedical Informatics, U of Kentucky

Abstract: Information overload of health consumers has become a ubiquitous problem in modern healthcare [1], especially for individuals with Chronic Rheumatic Diseases. CRDs, such as systemic lupus and vasculitis, often manifest with organ and life threatening symptoms. Management of CRDs focuses on patient education regarding diagnosis, disease course and long-term pharmacotherapy with immunosuppression. In particular, patients with CRDs are exposed to an endless flow of information, often at a rate far higher than their cognitive abilities can process it. To resolve the information overload issue, this project was to assess which data mining algorithms better perform effective and efficient data visualization using event-mined sequences in CRD context. CRD patients for diverse personal health information management (PHIM) outcomes including diagnostic, therapeutic, laboratory, and procedural codes were used to mine sequences and association patterns. According to our association rule mining result, management of all four types of systemic vasculitis involves an outpatient clinic visit, venipuncture and assessment of specific laboratory values for initial diagnosis, monitoring of disease activity and medication side-effects. Additionally, markers of inflammation, specifically ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein), are routinely checked and monitored in all forms of systemic vasculitis. Our PEM analysis indicates that the majority of the concepts extracted are classified as problems followed by treatment and testing. This result implies that current PEMs in clinical practice focus on medical diagnosis and therapeutic options rather than laboratory or clinical procedures that individual patients require.

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Abstracts

Poster Presentation #28

Abstract Title:	**categoryCompare: A Flexible Framework for Enrichment of Feature Annotations and Their Comparisons**
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Abstract: We have recently released a series of improvements to the next version of categoryCompare, a flexible framework for enrichment of feature annotations and comparisons between enrichment of annotations across two or more experimental groups. First, we have added the ability to use any type of gene or feature annotation. This means that enrichments can be calculated for any grouping of genes that can be generated by other means, including those from the Gene Ontology, KEGG and REACTOME pathways, groupings of GO terms such as those generated by GOCats (https://github.com/MoseleyBioinformaticsLab/GOcats), and from protein-protein interaction neighborhoods. Second, we have added methods that facilitate conversions from feature-annotation lists provided by users to the annotation objects used internally by categoryCompare. Third, we have created command-line executables for each stage of the typical categoryCompare analysis, which enable the use of categoryCompare by non-R programmers as well as interoperability with other tools and workflows. These improvements are available in version 2 of categoryCompare on GitHub at https://github.com/rmflight/categoryCompare2. Furthermore, we illustrate these improvements in several demonstration analyses.

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Poster Presentation #29

Abstract Title:	**A Pheno-Informatics Approach For Predicting Hospital Mortality In The Intensive Care Unit Using Serum Creatinine Trajectories**
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Abstract: Acute kidney injury (AKI) occurs in about 50% of ICU patients and is strongly associated with hospital mortality. Current approaches to model AKI severity focus on the maximal absolute or relative change in serum creatinine (SCr) in reference to baseline. However, the changes in SCr represent activities of a wide range of pathophysiologic processes in the same patient. It is thus difficult to characterize AKI solely based on SCr values. We develop a new pheno-informatics model to systematically identify AKI phenotype categories utilizing SCr trajectories over time in reference to changes in patient's clinical status and clinical treatments (i.e., acute renal replacement therapy) that can affect SCr interpretation. Our approach does not explicitly require a measured baseline SCr value for every patient, which is critical for AKI diagnosis but is often absent. Instead, we adopt a multi-interpolation method to compose SCr trajectories and develop a new dynamic time warping model to characterize the cumulative effect of AKI and to compare SCr trajectories. We utilize the hierarchical clustering to identify AKI phenotype categories in a large ICU dataset. Finally, we integrate AKI phenotypes with existing acute critical illness scores including SOFA and APACHE-II to enhance mortality prediction performance. Experimental results on 26,520 ICU patients at the University of Kentucky Albert B. Chandler Hospital indicate that our SCr trajectory-based AKI phenotype modeling is strongly associated with hospital mortality. We will further validate these findings and examine post-ICU outcomes in survivors.

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Poster Presentation #30

Abstract Title:	**?-Catenin Regulation of Skelatal Muscle Hypertrophy**
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Abstract: Purpose: Cytoplasmic free ?-catenin is tightly regulated as a downstream effector in the canonical Wnt signaling cascade, which is capable of implementing a cellular growth program during development and regeneration. A second and equally important function of ?-catenin involves linking the cell cytoskeleton with the transmembrane protein, cadherin, which binds to its counterpart in a neighboring cell, thereby forming stable intercellular connections known as adherens junctions. Previous studies suggest that Wnt signaling is intimately involved in the regulation myogenesis and muscle repair, and that ?-catenin may be a key contributor to hypertrophic growth in adult skeletal muscle. Methods: We generated an adult muscle-specific mouse model of tamoxifen-induced ?-catenin inactivation only in mature myofibers and not in satellite cells. We used a surgical model, synergist ablation, to induce mechanical overload on the plantaris muscle and cause robust hypertrophy within one week. Results: Loss of ?-catenin led to significantly blunted myofiber hypertrophy and a concomitant increase in satellite cell proliferation. Conclusion: ?-catenin and its interaction with cadherins on the myofiber side may be a necessary component of myofibers' mechanotransduction signals that controls satellite cell entry into the "Galert" phase and prepare resident stem cells for regeneration.

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Abstracts

Poster Presentation #31

Abstract Title:	**Mechanisms of Chronic Muscle Weakness in the Post-Sepsis Condition**
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Abstract: Sepsis is a life-threatening condition initiated when the immune system fails to contain a local infection and the infection spreads, triggering profound systemic inflammation that results in organ damage. With advances in critical care medicine, the sepsis survival rate has improved in recent years. Nearly 1.5 million sepsis survivors are discharged every year in the US, but they commonly suffer from chronic muscle weakness that significantly impacts their quality of life. However, mechanisms of post-sepsis muscle weakness are poorly understood due to the lack of a clinically relevant animal model. Here we adapted our ICU-like sepsis/resuscitation model and used ex vivo specific force analysis to show that late middle-aged murine sepsis survivors (C57BL/6) have skeletal muscle weakness one month after infectious insult, long after bacteremia was resolved. Evaluation of lean mass, wet tissue weight, and myofiber cross-sectional-area showed that muscle mass was recovered. Subsequent ultrastructural observation of skeletal muscle by transmission electron microscopy revealed enlarged mitochondria with gross morphological abnormalities in sepsis-surviving mice. In addition, respiration analysis and histochemical evaluation of mitochondrial enzyme activities revealed impaired mitochondrial function. As damaged mitochondria produce an abundance of free radicals, markers of protein oxidative damage (3-nitrotyrosine and protein carbonyls) were evaluated and found to be elevated in skeletal muscles of sepsis survivors for at least one month. Altogether, these novel findings indicate that long-term muscle weakness in sepsis survivors is accompanied by profound mitochondrial myopathy, which likely contributes to muscle dysfunction through decreased energy production, excessive free radical production, and unresolved protein damage.

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Poster Presentation #32

Abstract Title:	**Calcitriol Increases Complex II-Supported Oxygen Consumption and Expression of Lipolytic Genes in Human Skeletal Muscle Myotubes**
Author(s):	L. M. Bollinger, Department of Kinesiology and Health Promotion D. M Schnell, Department of Pharmacology and Nutritional Sciences D. T. Thomas, College of Health Sciences

Abstract: Mitochondrial oxygen utilization, particularly fatty acid oxidation, influences intramyocellular lipid content. Calcitriol, the active form of vitamin D, alters lipid partitioning and alters mitochondrial dynamics in skeletal muscle cells. Hypothesis: Calcitriol increases mitochondrial respiration and expression of lipolytic genes in cultured human skeletal muscle myotubes. Procedures: Primary Human Skeletal Muscle (HSkM) myotubes from 6 adult women were treated with 10nM calcitriol or vehicle (ethanol) control for 24h. Oxygen consumption rate (OCR), was measured (Agilent Seahorse XF24) using a mitochondrial stress test consisting of sequential treatments of oligomycin, FCCP, Rotenone + Succinate, and Antimycin A. Expression of lipid storage (DGAT1 and PLIN2), lipolytic activity (ATGL, CGI-58), and mitochondrial biogenesis (PGC-1?) genes were measured by RT-PCR. Statistical comparisons were made by paired t-test with ? = 0.05. Results: Calcitriol significantly increased OCR in response to Rotenone + Succinate by 2.1 fold ($p = 0.012$), but did not alter OCR under any other conditions. Additionally, calcitriol significantly increased expression of the lipolytic gene CGI-58 (2.0 fold, $p = 0.007$) and tended to increase expression of PGC-1a (1.7 fold, $p = 0.07$). Calcitriol did not significantly impact expression of ATGL, DGAT, or PLIN2. Conclusions: Calcitriol increases OCR supported by electron transport chain (ETC) complex II and increases expression of genes involved in lipolysis and mitochondrial biogenesis. These data are consistent with an increased lipolytic supply of FADH2 to the ETC. Future work will focus on elucidating the effects of calcitriol on lipolysis, mitochondrial biogenesis, and fatty acid oxidation within human skeletal muscle myotubes.

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Abstracts

Poster Presentation #33

Abstract Title:	**Inhibition of integrin ?5?1 with the small peptide ATN-161 reduces infarct volume and improves functional recovery through reduction of blood-brain barrier permeability**
Author(s):	D. N. Edwards, Department of Neuroscience, U of Kentucky K. Salmeron, Department of Neuroscience, U of Kentucky J. F. Fraser, Department of Neurosurgery, U of Kentucky G. J. Bix, Department of Neurology, U of Kentucky

Abstract: Stroke is a leading cause of death and disability with limited therapeutic options. We have demonstrated that the endothelial cell-selective ?5?1 integrin (a fibronectin receptor expressed in development, but not adult cerebrovasculature under physiologic conditions) knockout mice are profoundly resistant to changes in blood-brain barrier (BBB) integrity and brain injury after ischemic stroke. Therefore, we hypothesize that therapeutic inhibition of ?5?1 would result in a more intact BBB, thus reducing infarct volume and improving functional recovery. Wild-type mice underwent transient middle cerebral artery occlusion, and by post-stroke day (PSD) 2, we noted a significant increase in penumbral ?5?1 cerebrovascular expression (by immunohistochemistry) that exponentially increased until PSD4, limited to the luminal compartment of vasculature. Inhibition of ?5?1 with the small peptide ATN-161 (1mg/kg; IP) administered immediately after reperfusion, PSD1, and PSD2 resulted in significantly smaller infarcts (TTC and MRI at PSD3), improved functional recovery (Neuroscore through PSD14) and a stabilized BBB (MRI with gadolinium contrast and qPCR at PSD3). Finally, in vitro brain endothelial cell monolayer permeability studies demonstrated that oxygen-glucose deprivation and TNF- ? treatment increased permeability (FITC-dextran migration measurements) and decreased cell-surface expression of the tight junction protein claudin-5, changes that could be prevented by ATN-161. Collectively, our results demonstrate that endothelial cell ?5?1 expression increases acutely after stroke in the luminal compartment, may contribute to BBB breakdown and subsequent expansion of brain injury via modulation of tight junction protein function, and could represent a novel therapeutic target for ischemic stroke.

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Poster Presentation #34

Abstract Title:	**An Epigenetic Approach for the Modulation of Amyloid Precursor Protein (APP) Processing in Alzheimer's Disease**
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Abstract: Alzheimer's disease (AD) is a multifactorial ailment for which current therapeutics remain insufficient to broadly address the underlying pathophysiology. Because epigenetic gene regulation can affect multiple gene and protein pathways, including those involved in AD, we hypothesized that a single epigenetic modulating drug would simultaneously affect the expression of a number of AD-related gene targets. Using an AD cell model over-expressing APP with the Swedish mutation (HEK/APPsw), we screened our in-house library of epigenetic drugs to identify non-toxic small molecules that significantly reduced ?-amyloid (A?). Candidate compounds were confirmed with A? ELISA. Then, using real time quantitative polymerase chain reaction (RT-qPCR) and western blots, we analyzed the effects of the small molecules on AD-relevant gene and protein expression. We identified a small molecule histone deacetylase inhibitor, M344, that is non-toxic, reduces A?, and alters the expression of multiple AD-related genes. Of note, M344 decreases amyloidogenic ?-secretase (BACE) gene expression. Additionally, M344 increases the expression of BDNF, a-secretase (ADAM10), MINT2, FE65, and other AD-relevant genes. M344 also increases sAPPa and CTFa metabolite production, both cleavage products of ADAM10, concordant with increased ADAM10 gene expression. M344 also increases levels of immature APP, supporting an effect on APP trafficking, concurrent with the observed increase in MINT2 and FE65, both shown to increase immature APP. Using an epigenetic approach, we show that it is possible to use a single drug compound to simultaneously affect the expression of key AD and neuroprotective genes.

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Poster Presentation #35

Abstract Title:	**Novel Applications of MRI Techniques in the Detection of Neuronal Dysfunction before Tangle Pathology in Tau Transgenic Mice**
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Abstract: Background: Tauopathic patients have significant cognitive decline accompanied by severe, irreversible brain atrophy. Neuronal dysfunction is thought to occur years before diagnosis. A major obstacle in the treatment of tauopathies is that current diagnostic tools are ineffective at detecting pre-pathological changes. We previously developed a MEMRI (manganese-enhanced magnetic resonance imaging) protocol coupled with R1-mapping to measure the extent of neuronal dysfunction that occurs before appearance of cognitive deficits and tau pathology associated with the rTg4510 tau model. In this study, we performed MEMRI with mangafodipir, an FDA-approved contrast. Methods: We used MEMRI to measure neuronal dysfunction in rTg4510 mice tau transgenic mice at 2 months (no pathology/cognitive deficits), and 3 months (presymptomatic pre-tangle pathology detectable). We measured MEMRI R1 changes before (baseline) and after (time-course) injecting mangafodipir (50mg/kg) intraperitoneally. We focused on the superior cortex and hippocampal sub-regions. Results: We found mangafodipir to be an effective contrast for MEMRI of mouse brains. Optimal enhancement of the cortex and hippocampus occurs 12-24 hours post-injection. Functional changes were detectable in transgenic mice at two months. Conclusions: This study builds upon our previous work showing that MEMRI (with MnCl2) reveals important functional differences between tau transgenic and non-transgenic mice. Here we found that mangafodipir is at least as effective as MnCl2 in performing MEMRI, detecting differences at an earlier time point. Mangafodipir exhibits less toxicity than MnCl2 due to structural similarity to EDTA (used to treat manganese toxicity), making mangafodipir a target for translation of MEMRI for tauopathy into human subjects.

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Poster Presentation #36

Abstract Title:	**CLARITY for 3-D In Vivo Imaging of the Neurovascular Unit**
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Abstract: CLARITY is a newly developed tissue clearing method used for the transformation of biological tissue into a tissue-hydrogel hybrid, enabling highly detailed images of the brain's cellular structure. Historically, imaging studies have been limited to small regions of the brain or do not allow for staining of relevant proteins or genes. CLARITY uses an acrylamide hydrogel to maintain the structural organization of proteins and nucleic acids and surfactant-assisted delipidation to render the tissue permeable to immunostaining and suitable for detailed microscopic analysis. For our studies, we used the X-CLARITY™ System from Logos Biosystems. Male CD-1 mice were anesthetized; the thorax was opened; and an infusion needle was placed into the left cardiac ventricle to perfuse the brain with PBS and paraformaldehyde. Whole brain was collected and fixed in paraformaldehyde. After washing with PBS, brains were either processed as a whole or sliced into sections. Brain tissue was placed in hydrogel solution and hybridized utilizing the X-CLARITY™ Polymerization System. Once hybridized, lipids from the tissue were removed through electrophoresis with ionic detergents using the X-CLARITY™ Tissue Clearing System. After clearing, the neurovasculature was stained with collagen IV primary antibody followed by incubation with Cy3-conjugated secondary antibody. In addition, we cleared the brains of mice with YFP-labeled neurons. Cleared brain tissue was imaged using a Nikon A1R inverted confocal microscope. We are currently using CLARITY with single- and two-photon microscopy imaging to examine the spatial relationship between cells of the neurovascular unit in animal models of neurodegenerative and neurological disorders.

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Poster Presentation #37

Abstract Title:	**Differential Susceptibility of Large-Scale Brain Networks to White Matter Alterations in Aging**
Author(s):	C.A. Brown, Department of Neuroscience, U of Kentucky C.D. Smith , Department of Neurology, U of Kentucky B.T. Gold, Department of Neuroscience, U of Kentucky

Abstract: Introduction: Older adults experience significant alterations in white matter (WM) structure during aging. Most studies examining these measures have focused on whole brain or single tract-focused approaches to quantify these alterations. However, it is unclear how these alterations differentially affect various large scale brain networks, such as the default mode network (DMN), dorsal attention network (DAN), or fronto-parietal control network (FPCN). In this study, we investigated the differential effects of WM alterations within and between these large-scale brain networks. Methods: 66 cognitively normal older adults (ages 60-92) underwent diffusion tensor imaging (DTI) and FLAIR imaging. Probabilistic tractography was performed to generate group templates of WM pathways within each network (DMN, DAN, FPCN) and between each network (i.e. DMN to DAN). WM hyper-intensities (WMHs) were identified in FLAIR images using an automated approach. Fractional anisotropy (FA) and WMH volume were measured within each WM template. Repeated-measures ANOVA was performed to examine whether there was a significant WM template × age interaction for either FA or WMH volume. Results: There was a significant WM template × age interaction for WMH volume ($F_{5,60} = 3.35$, $p = .01$) but not for FA ($F_{5,60} = 1.36$, $p = .25$). Follow-up analyses demonstrated that the following pattern for the strength of positive correlations between age and WMH volume: DAN > FPCN = DAN to FPCN > DMN to FPCN = DMN to DAN = DMN. In contrast, FA values across all WM templates were negatively associated with age to a similar degree. Conclusions: WMH volume, but not WM microstructure, is differentially affected across large-scale brain networks in aging. The DAN and FPCN appear to show greater WMH volume with increasing age, while the DMN shows the least. Future work should investigate whether the differential susceptibility of these networks to accumulating WMHs is associated with cognition.

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Abstracts

Poster Presentation #38

Abstract Title:	**Biochemical and Immunofluorescent Propertiees of Proteopathic alpha-Synuclein in Synucleinopathies**
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Abstract: Objective: Determine whether biochemical differences exist in alpha-synuclein found in Parkinson's disease (PD) and multiple system atrophy (MSA). Background: In synucleinopathies such as PD and MSA there is growing support for the idea that different conformations of alpha-synuclein exist. In prior studies we found alpha-synuclein seeding ability present in both PD and MSA brain extracts using a cell-based FRET assay (Holmes and Furman, PNAS 2013). Here we test biochemical properties and antibody-binding of alpha-synuclein in these two diseases. Methods: Brain tissue was serially extracted from twp different regions from patients with PD (n=9) and MSA (n=10) to yield buffer-soluble and detergent-insoluble fractions. We utilized immunoprecipitation methods with multiple antibodies that bind to different epitopes of alpha-synuclein to determine a binding profile for alpha-synuclein in these samples. We also used immunoblot and immunofluorescence to assess phosphorylated and ubiquitinated forms in samples from these patients. Results: There were distinct differences in the ability of various antibodies to bind to alpha-synuclein from PD vs MSA. Both commercial and novel antibodies were able to bind a form of alpha-synuclein which was capable of seeding synuclein aggregation in the cell-based assay from MSA samples, but only minimally from PD samples. Immunoblot studies showed high levels of alpha-synuclein in both soluble and insoluble fractions, but aggregation ability as measured on the FRET assay did not correlate with total synuclein levels or phosphorylated synuclein levels. Immunofluorescence did show that aggregated synuclein inclusions within biosensor cells co-localize with markers for the amyloid state. Conclusion: Antibody binding differences in pathologic alpha-synuclein in PD and MSA support the idea of conformational differences in the aggregated state. Further biochemical characterization suggests that this difference is not driven by phosphorylated or ubiquitinated forms of synuclein.

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Abstracts

Poster Presentation #39

Abstract Title:	**Neuroprotective strategies following severe controlled cortical impact traumatic brain injury: lipid peroxidation-derived neurotoxic aldehyde scavenging and inhibition of mitochondrial permeability transition**
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Abstract: Traumatic brain injury (TBI) represents a significant health crisis in the United States. Currently there are no neuroprotective FDA-approved pharmacotherapies for TBI. Due to the complex pathophysiology which occurs following TBI, more robust pharmacological approaches must be developed. Mitochondrial dysfunction and the formation of neurotoxic aldehydes contribute extensively to TBI pathology, making them promising therapeutic targets for prevention of cellular death and dysfunction following TBI. The following are evaluated. 1) The neuroprotective effect of cyclosporine A (CsA), on synaptic and non-synaptic mitochondria. Mitochondria are heterogeneous, consisting of both synaptic and non-synaptic populations, which have distinct properties. Our results indicate that compared to non-synaptic mitochondria, synaptic mitochondria sustain greater damage 24h following severe controlled cortical impact injury in young male rats, and are protected to a greater degree by CsA, an FDA-approved immunosuppressant, capable of inhibiting mitochondrial permeability transition. 2) The neuroprotective effects of a 72h subcutaneous continuous infusion of CsA combined with phenelzine (PZ), an FDA-approved monoamine oxidase inhibitor (MAOI) class anti-depressant capable of scavenging neurotoxic aldehydes. Our results indicate that individually CsA or PZ attenuate neurotoxic aldehyde formation, PZ maintains mitochondrial respiratory control ratio and cytoskeletal integrity, but together, PZ and CsA, do not maintain neuroprotective effects. 3) The ability of PZ (aldehyde scavenger and MAOI), to attenuate cognitive dysfunction following TBI compared to hydralazine (aldehyde scavenger) and pargyline (MAOI), in an attempt to further elucidate the role PZ's MAOI mechanism of action has in TBI pathophysiology.

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Poster Presentation #40

Abstract Title:	**Parietal Lobe Cerebral Microbleeds Are Associated with Lower Cerebrospinal Fluid Beta Amyloid 1-42 in Patients with Sporadic AD**
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Abstract: Background: Cerebral microbleeds (CMBs) are considered to be an imaging marker for cerebral small vessel disease. Recent evidence also suggests that white matter hyperintensities (WMHs) located in posterior brain regions are associated with Alzheimer's disease (AD). The current study was designed to explore if there is a similar trend of associations between CMBs and AD. Methods: Measures of CMBs were collected from 62 participants who had CSF sampling. CSF A?1-42 levels (a surrogate for AD), were measured. FLAIR and GRE MRI sequences were obtained to assess WMHs and CMBs. CMBs were visually rated using MARS scale. Partial correlation and linear regression analyses were conducted to examine the association of lobar CMBs with AD. Results: Mean age was 74.9 ± 7.4 years, 45% were male and the mean years of educational attainment were 16.9 ± 3.1 years. Partial correlation analyses showed an association between parietal lobe CMBs and lower CSF levels of A?1-42 (rho = - 0.27, p = 0.04). CMBs in the frontal, temporal and occipital lobes were not correlated with the CSF levels of A?1-42. Linear regression analysis demonstrated that parietal lobe CMBs were strongly associated with lower CSF levels of A?1-42 (p = 0.04, beta = - 0.29). Conclusion: Parietal lobe CMBs showed a strong association with lower CSF A?1-42, providing evidence that CMBs in the parietal lobe represent a potential surrogate imaging biomarker for sporadic AD. Additional studies examining the association of lobar CMBs with regional WMHs and specific patterns of cognitive decline are under investigation currently.

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Abstracts

Poster Presentation #41

Abstract Title:	**Delayed brain responses discriminate malingered individuals from patients with brain injury**
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Abstract: Traumatic brain injury (TBI) is a major public health concern in the United States, affecting up to 1.7 million people every year. Neuropsychologists report that up to 40% of individuals undergoing evaluations for TBI may be malingering neurocognitive deficits. This indicates a need for more reliable tests for validating TBI while identifying malingerers. In this study, memory-related brain potentials were compared between moderate or severe TBI and malingered neurocognitive deficit (healthy age-matched) and reaction times of honest (n=12), malingering (n=15), and brain injured (n=14) individuals during a memory recognition task. Scalp signals were recorded with a 32 channel scalp EEG cap. A major event related potential signal indicative of cognitive processing P3, or late positive component, was analyzed using EEGLAB. Bilateral P3 fractional latencies of frontal scalp sites were compared between the three groups for both old and new tasks. Results show a significant delay in P3 during old tasks in malingerers when compared to brain injured subjects in central and left frontal electrodes FZ, FP1, F3, F4 and F7. A significant delay was also shown in P3 during old tasks in malingerers when compared to honest subjects in left frontal electrodes F3, F4, and F7. These results, along with previous reported reaction time delay, indicate that additional processing time and effort in the brain activity of malingering individuals are measurably different from those of honest and brain injured individuals.

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Poster Presentation #42

Abstract Title: **Reading aloud improves working memory related frontal theta oscillations in older adults**

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Abstract: We previously reported that two different cognitive interventions (reading aloud and origami practice) improved memory performance in cognitively normal older adults. Both tasks exercise working memory, and successful working memory manipulation has been associated with increased frontal theta power as detected by EEG. Here we test the hypothesis that these tasks increased theta power during the intervention to improve working memory performance. We randomly assigned 36 cognitively-normal participants over age 65 to a reading, an origami, or placebo group over the course of eight weeks. Pre- and post-intervention EEG signals were collected as participants performed the Bluegrass Short-Term (BeST) memory task. Changes in theta power in frontal-lobe and parietal-lobe leads were analyzed and compared to performance on the BeST task and neuropsychology tests. Participants in the reading group showed increases in theta power in the left frontal ($0.009uV^2$, $p=0.028$), right frontal ($0.008uV^2$, $p=0.028$), left parietal ($0.005uV^2$, $p=0.017$), and right parietal ($0.008uV^2$, $p=0.013$) leads, while participants in the origami group did not. Participants in the control group showed an increase in the left frontal lead ($0.005uV^2$, $p=0.041$). Of note, theta power changes in bilateral frontal sites were associated with FCSRT (Frontal Left $b=175$, $p=0.05$, Frontal Right $b=245$, $p=0.009$) but not MOCA scores. Our results suggest that reading intervention may have enhanced performance on cognitive tasks by increasing working memory performance mediated by theta waves in the frontal lobe. Future analyses will examine post-intervention alpha and gamma changes to see how they mediate improved cognitive functioning from reading aloud or origami practice.

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Poster Presentation #43

Abstract Title:	**Mild Traumatic Brain Injury Dysexecutive Clusters with Olfactory Symptoms**
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Abstract: Traumatic brain injury (TBI)'s link to olfactory deficits has been identified in the literature, but its structural mechanism and related clinical sequelae remain difficult to track.1-4 Given the olfactory mechanism's proximity to orbitofrontal cortex in the brain, executive functions are hypothesized to be affected by TBI when olfaction is also affected. This study evaluated symptom clusters in mild TBI (mTBI) patients with self-reported diminished olfaction after injury, to evaluate the link between orbitofrontal functions and olfactory mechanism in mTBI. Among the abstracted and deidentified medical charts of mTBI patients of the Kentucky Neuroscience Institute, 19 mTBI patients reported experiencing dysosmia following injury. Fischer's Exact test was used to test for association between categorical variables. All analyses were conducted using SPSS v24 with an alpha level of 0.05. Among self-reported dysosmic patients, reported processing speed deficits were significantly associated between attention difficulties, short-term memory deficits, expressive language difficulties, and disordered sleep (Ps < 0.05). Patient reported irritability and aggression symptoms were significantly associated with attention difficulties, short-term memory deficits, anxiety, depression, and emotional lability (Ps < 0.05). Patient reported language difficulties were significantly associated with short-term memory deficits and disordered sleep (Ps < 0.05). Additionally, patient reported emotional lability was significantly associated with fatigue (p = 0.04). Results suggest that mTBI patients with self-reported diminished olfaction report a myriad of dysexecutive symptoms. Olfaction as a clinical marker to assess dysexecutive syndrome in neurotrauma should be further explored.

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Poster Presentation #44

Abstract Title:	**Memory-Related Brainwaves in Older Adults are Associated with Both Cognitive Ability and Vascular Risks**
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Abstract: Currently, there is limited understanding on cerebrovascular disease (CVD) risk and neural correlates of CVD induced cognitive impairment in older adults. Our previous study revealed that vascular risk factors (e.g. BPSYS) positively correlated with neural repetition during a short-term memory task at the bilateral frontal sites (e.g. F3 & F4). Here, we tested the hypothesis that brain activity during memory task is associated with cognitive ability (measured by neuropsychological tests) and vascular risk factors. 64-channel electroencephalography (EEG) were recorded from 19 older adults (mean age 75.3) from the community-based aging cohort, UK Alzheimer's Disease Center. Neuropsychological tests e.g. Animal naming, Digit Span Backward (DIGIB), Trail-making A&B, and Digit Symbol (DSYM) were performed to evaluate subjects' cognitive status. We found that several neuropsychological scores were significantly correlated with brain signals associated with learning rate of memory target (Match), and non-targets (non-match). ANIMALS significantly negatively correlated with the right frontal F4 ($p < 0.001$) for Match, while DIGIB significantly correlated with the right posterior P4 ($p < 0.01$). BPSYS positively correlated with both the left and right frontal, respectively F3 and F4 at target match. At target non-match, BPSYS positively correlated with the left and right posterior cognitive ERPs, respectively C3 and C4. The present results revealed that increased brain activity during learning and memory at the bilateral frontal and parietal sites are correlated with lower cognitive functions. Additionally, higher blood pressure as vascular risk factor is associated with increased brain functions. Thus, high blood pressure indirectly associated with lower cognitive functions.

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Poster Presentation #45

Abstract Title:	**Elucidating Subtypes and Risk Factors of Brain Arteriolosclerosis**
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Abstract: Cerebrovascular pathologies are often seen in aged brains. Here, we focus on brain arteriolosclerosis (B-ASC), i.e., degenerative thickening of cerebral arterioles. We recently reported that severe B-ASC pathology is associated with global cognitive status (PMID 26738751). To study risk factors of B-ASC, we analyzed 2,390 cases with clinical and neuropathological autopsy data from the National Alzheimer's Coordinating Center. Cases were analyzed according to age at death (< 80 years and ? 80 years) using logistic regression modeling. Gender was associated with B-ASC pathology in both age at death groups after controlling for covariates including age at death, and conventional vascular risk factors: hypertension, diabetes, smoking, and hypercholesterolemia. In a subset of cases with genetic information (n = 925), the ABCC9 gene variant (rs704180), previously associated with hippocampal sclerosis, was also associated with B-ASC pathology in the ? 80 year-old group. To address in finer detail the heterogeneous arteriolar morphologies that could be classified as B-ASC, we analyzed 74 cases from the University of Kentucky Alzheimer's Disease Center (UKADC) and UK Pathology Department. Within this convenience sample, the median age at death was 56.5 years with a range of 20 – 96 years. One of the subtypes of B-ASC pathology in this cohort consisted of arteriolar profiles with multiple internal lumens, which we refer to as multi-lumen vessels (MLVs, which generally have ? 3 lumens in a single vascular profile). In this sample, 62.1% (n = 46) of cases had ? 5 MLVs per brain section, as operationalized using CD34 immunohistochemistry in the frontal neocortex (Brodmann area 9). Interestingly, MLV densities increased with advanced age of death ($r = 0.51$; $p < 0.0001$). We conclude that B-ASC is a complex pathologic phenotype in advanced age with both genetic and clinical risk factors, as well as morphologic subtypes, that require further study.

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Abstracts

Poster Presentation #46

Abstract Title:	**Identifying Predictive Fluid Biomarkers for White Matter Hyperintensities (WMH) and Cognitive Impairment in Vascular Cognitive Impairment and Dementia (VCID)**
Author(s):	T. L. Sudduth, Sanders-Brown Center on Aging, U of Kentucky Z. S. Winder, Department of Physiology, U of Kentucky D. M. Wilcock, Department of Physiology, U of Kentucky

Abstract: Vascular cognitive impairment and dementia (VCID) is the second leading cause of dementia and often occurs co-morbidly with Alzheimer's disease (AD). Currently diagnosis for VCID is limited to clinical signs of cognitive impairment partnered with vascular injury seen most often as white matter hyperintensities (WMH) on MRI neuroimaging. There is a growing need in the research and clinical communities to develop an earlier and more accurate diagnosis of VCID. This project seeks to identify fluid biomarkers in CSF and blood collections, which can help to act as early markers for VCID. Our preliminary data looked primarily at the cross-sectional results of CSF and blood samples collected from patients in our MCI-CVD (Mild Cognitive Impairment-Cerebrovascular Disease) cohort using MSD V-PLEX assays to measure levels of 4 possible biomarkers (TNF?, IL-12, PIGF, VEGF-D) along with other inflammatory and angiogenic proteins. The future plans for this project will look towards determining the correlation of these biomarkers to longitudinal clinical progression as well as pathologic changes as seen with neuroimaging. In addition we hope to make use of machine learning to help us better predict a diagnosis of VCID with the fluid biomarkers seen in our CSF and blood samples.

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Abstracts

Poster Presentation #47

Abstract Title:	**APOE, Metabolism and Cognitive Function: An Assessment via Indirect Calorimetry**
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Abstract: The gene Apolipoprotein E (APOE) encodes for three isoforms in the human population (E2, E3, and E4), and the E4 isoform – carried by approximately 1/5 of the population – is the strongest genetic risk factor for late onset Alzheimer's Disease (AD). Both AD and E4 have been associated with impaired brain metabolism. Our preliminary data show that aged mice expressing human E4, and not E3, demonstrate a metabolic "shift" reflected as a preference for lipids vs carbohydrates as a fuel source. We hypothesize that similar apoE differences are present in cognitively normal individuals, and therefore aim to translate these findings to human subjects. We believe an E4-directed shift away from carbohydrate utilization may represent a critical step in the progression of cognitive decline, and thus a potential novel biomarker for AD risk. To test our hypotheses, we aim to measure metabolic rate and respiratory quotient (RQ) using indirect calorimetry (IC). Real-time metabolic measures will be assessed in individuals with various APOE genotypes – both at rest and during a cognitive and dietary challenge. Interpretation of RQ will be aided by measuring adiposity, blood glucose, and urinary urea nitrogen. Initial feasibility studies show measurable increases in RQ during a cognitive challenge, as well as a trend toward increased resting energy expenditure. Additionally, an acute dietary challenge resulted in a steady increase in RQ following ingestion. We hope to expand our methods to measure elderly subjects (cognitively normal, mild cognitive impairment and AD), as well as potential collaborative efforts in other areas of neuroscience.

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Poster Presentation #48

Abstract Title:	**Human Adipose Beiging in Response to Cold and Mirabegron**
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Abstract: The induction of beige adipocytes in subcutaneous white adipose tissue (SC WAT) depots of humans is postulated to improve glucose and lipid metabolism in obesity. Here we analyzed the capacity of lean and obese, insulin-resistant subjects to induce UCP1 and TMEM26 in SC WAT in response to cold (30 min ice application each day for 10 days of the upper thigh) or treatment with the ?3 agonist Mirabegron. Cold significantly induced UCP1 and TMEM26 protein in both lean and obese, insulin-resistant research participants, and this response was not inhibited by age. Interestingly, these proteins increased to the same extent in the non-iced contralateral leg, indicating a crossover effect. We further analyzed the bioenergetics of purified mitochondria from the abdominal SC WAT of cold-treated subjects and determined that repeat ice application significantly increased uncoupled respiration, consistent with the UCP1 protein induction and subsequent activation. Cold also increased state 3 and maximal respiration, and this effect on mitochondrial bioenergetics was stronger in the summer than winter. Finally, we determined whether chronic treatment (10 weeks) with the ?3 agonist Mirabegron induced beige adipose tissue in obese subjects. This treatment increased UCP1, TMEM26, and CIDEA in obese subjects. In conclusion, cold or ?3 agonists cause the induction of beige adipose in tissue human SC WAT: this phenomenon may be exploited therapeutically in older, insulin-resistant, obese individuals.

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Abstracts

Poster Presentation #49

Abstract Title:	**Investigating the Effects of Timed Exercise on Metabolism**
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Abstract: The human circadian system synchronizes physiology and behavior with the environment. Modern lifestyles, including nighttime light exposure and early morning alarm clocks, interrupt this synchronization resulting in circadian misalignment. Improperly aligned circadian rhythms are associated with obesity and metabolic dysfunction. Thus, implementing an intervention to correct this alignment is a novel way to treat these deleterious health conditions. It is known that physical activity changes the timing of the circadian clock. Our preliminary data suggests that evening exercise alters the phase (timing) of the internal clock. The goals of this study are to determine if evening exercise alleviates circadian misalignment and improves metabolism. Sedentary men and women (BMI>18.5; ages 18-45 years) will be randomized to either morning or evening exercise (relative to internal clock time) at 70% VO2max, 5 days per week for 4 consecutive weeks. We will measure circadian and metabolic parameters before and after the exercise intervention. Circadian misalignment will be calculated as the duration between the phase of the internal clock and sleep. We predict evening exercise will advance the timing of the circadian clock, resulting in a reduction in circadian misalignment. We predict participants exercising in the evening, compared to morning, will also have improved insulin sensitivity, plasma lipids, blood pressure and body composition. This study will identify the best time of day to exercise and could thereby improve the efficacy of exercise regimens.

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Poster Presentation #50

Abstract Title:	**Cooking classes and dietary change in rural Appalachia**
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Abstract: Introduction: In rural Appalachia, rates of diet-linked diseases including hypertension, diabetes, cardiovascular disease, and cancer are all significantly higher than in other regions of the nation. Suboptimal dietary intake stems from a web of individual, interpersonal, social, and structural factors including taste preferences, peer influences, cultural patterns, food cost and access. Methods: When local residents identified lack of cooking skills as a significant barrier to healthy eating, we developed a multi-component, community-engaged dietary intervention that included six weekly cooking classes held in community centers. Questionnaires were administered at baseline, 3-weeks post intervention and 3-months post intervention to assess participants' barriers to healthy eating, food purchasing practices, cooking skills and adherence to nutritional guidance. We used a pre-test, repeated measures follow-up design with one group. Friedman's tests and Wilcoxon signed rank tests were used to compare participants' responses across time. Results: Eighty-five adults, ages 15-75, who regularly cooked for children participated in this study. Nearly half (43%) of participants indicated their household income was below $10,000. Results demonstrated statistically significant improvements in dietary behavior, including fewer barriers to eating healthfully, decreased consumption of fast food and unhealthy snacks, and increased use of nutritional information. Most improvements were sustained or even enhanced three months after class completion. Discussion: Acquisition of cooking skills and experience was associated not only with improved dietary attitudes and behavior, but also with decreased barriers to eating healthfully. Impressive in any population, these findings are particularly promising given participants' low-income levels and the modest sample size.

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Poster Presentation #51

Abstract Title: **FOS is a Critical Transcription Regulator Necessary for the Ovulatory Process in Humans**

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Abstract: FOS (a.k.a, c-fos) is a subunit of the activator protein-1 (AP-1) transcription factor and acts as heterodimeric complexes via binding with one of the Jun proteins (JUN, JUNB, JUND). Fos null mice failed to ovulate and form a corpus luteum (CL) even when given exogenous gonadotropins, indicating that ovarian Fos expression is critical for successful ovulation and CL formation. Our previous study demonstrated that the expression of FOS and Jun proteins (JUN, JUNB, JUND) increases in dominant follicles after hCG administration in normally cycling women. However, nothing is known about the regulatory mechanism involved in the expression of these transcription factors and their functions in human ovulatory follicles. In the present study, we utilized a primary human granulosa/lutein cell (hGLC) culture model that mimics key aspects of in vivo changes of periovulatory gene expression such as PGR, EGF-like factors (AREG and EREG), and PTGS2 in humans. To determine the regulatory mechanisms controlling the expression of FOS and Jun proteins, hGLC was cultured with or without hCG for various time points. qPCR and Western blot analyses showed a transient and biphasic increase in levels of mRNA and protein for FOS, which peaked at 1-3 h after hCG stimulation, declined to the time 0 h value by 6 h, and then increased again at 12 h. hCG also increased the level of JUN, JUNB, and JUND protein at all time points examined. To determine whether FOS is present as heterodimeric complexes with one of the Jun proteins, hGLC were cultured with or without hCG for 3 h and used for co-immunoprecipitation (Co-IP) analysis. Co-IP data showed that FOS interacts with all Jun proteins in hCG-treated cells, indicating that there are at least 3 different forms of FOS/AP-1 complexes in hGLC. To determine the role of FOS, hGLC was treated with or without T-5224 (a specific FOS inhibitor) in the absence or presence of hCG for various time points. T-5224 treatment inhibited hCG-induced increases in the expression of PGR, prostaglandin E synthase (PTGES), and prostaglandin transporters (SLCO2A1 and ABCC4). To determine whether FOS/AP-1 directly regulates the expression of these genes at the DNA level, ChIP assays were conducted using chromatin samples extracted from hGLC cultured with hCG. PCR results showed that chromatin fragments containing FOS/AP-1 binding sites in the promoter region of these genes were enriched in hGLC. In summary, these data together demonstrated that hCG increases the expression of FOS/AP-1 transcription factors, which in turn regulates the expression of key ovulatory genes such as PGR, PTGES, SLCO2A1 and ABCC4 by directly binding to the promoter regions of these genes in hGLC. As the up-regulation of PGR and prostaglandins in periovulatory follicles is pivotal for successful ovulation, the present findings indicate that FOS/AP-1 transcription factors play an essential role in ovulation by regulating the expression of specific ovulatory genes in humans.

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Center for Clinical and Translational Science

Abstracts

Poster Presentation #52

Abstract Title:	**Joint fluid after anterior cruciate ligament rupture reflects a rheumatoid arthritis-like inflammatory state**
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Abstract: Purpose: Evaluate changes in synovial fluid proteome following acute anterior cruciate ligament injury. Design: Arthrocentesis performed twice on 6 patients with acute ACL tears at 6 and 14 days post injury. Synovial fluid was analyzed for type II collagen degradation and by a highly multiplexed protein assay. Primary analyses focused on analytes previously linked to osteoarthritis (OA) and rheumatoid arthritis (RA). Biomarker values at the 2 time points were compared using paired t-tests and standardized response means (SRM) to evaluate trends over time. In addition, pathway analysis was performed by entering all corresponding genes with an SRM > 1.00 into the DAVID bioinformatics database. Results: Chondrodegnerative enzymes and products of cartilage degeneration consistent with OA all increased over time following injury: MMP-1 (p=0.08, SRM=1.00), MMP-3 (p=0.05, SRM=0.90), ADAM12 (p=0.03, SRM=1.31), aggrecan (p=0.08, SRM=1.13) and CTX-II (p=0.07, SRM=0.56). In addition, we also observed large increases in 7 markers previously indicated in the onset and/or severity of RA. Those corresponding genes were associated with 8 pathways, notably the cytokine-cytokine receptor interaction (p=0.003) and osteoclast differentiation pathways (p=0.01). Discussion: To our knowledge, this is the first clinical study to assess proteomic changes following acute ACL injury. We found that the protein responses post-injury were similar to those previously reported in OA, but also contained large increases in RA associated markers, suggesting changes in the synovial proteome consistent with an inflammatory arthritogenic process post-ACL injury. These results highlight the potential of identifying new therapeutic targets to mitigate the early onset of progressive chondrodegeneration following acute ACL tear.

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Poster Presentation #53

Abstract Title:	**PAR4 Activation as a Persistent Model of Bladder Pain: Role of MIF and HMGB1**
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Abstract: Painful bladder syndrome/interstitial cystitis (PBS/IC) is characterized by bladder-related pain without urinary infection or other bladder pathology. We showed that activation of intravesical protease activated receptor 4 (PAR4) induced acute bladder pain without other signs of inflammation and this effect was mediated through macrophage migration inhibitory factor (MIF) and high mobility box group 1 (HMGB1). We extended this model by using repeated PAR4 instillation to elicit persistent bladder pain. We hypothesized that MIF and HMGB1 also mediate persistent bladder pain. Female C57BL/6 mice received intravesical instillations of PAR4 (100μM, for one hour) 3 times every other day and abdominal mechanical hypersensitivity (50% mechanical threshold) was tested before first PAR4 injection (baseline) and at days 1, 2, 3, 4, 7 and 9 after first PAR4 injection. Micturition changes were measured and bladders were examined for histological changes. MIF antagonist (MIF098; 40 mg/kg; i.p.; bid) or HMGB1 inhibitor (glycyrrhizin; 50 mg/kg; i.p.; daily) were administered daily starting from day 2 until day 8 after first instillation. There was a significant and persistent decrease in abdominal mechanical threshold starting from day 3 until day 9. Glycyrrhizin fully reversed while MIF098 partially reversed abdominal mechanical hypersensitivity starting on day 3 after first PAR4 instillation and analgesic effects lasted throughout rest of testing period. None of the groups had significant micturition change and overt histological changes. Repeated intravesical PAR4 instillation produced persistent bladder pain without overt bladder inflammation. MIF and its signaling downstream (HMGB1) are two effective target molecules for bladder pain alleviation.

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Poster Presentation #54

Abstract Title: **Development of Dry Eye Symptoms and Corneal Sensitivity after Ocular Surgeries.**

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Abstract: Ocular surgery can introduce injury to the surface of the eye. Although a common post-operative condition is dry eye syndrome, ocular neuropathic pain can also develop. Pathology behind neuropathic pain may include failure to develop or maintain constitutive activity of mu opioid receptors (MORCA). In a recent study using mice, we showed that corneal surface injury (CSI) caused increased pain behavior (eye wiping) in response to a mild NaCl stimulus when compared to control uninjured mice. We also demonstrated that systemic treatment with naltrexone after resolution of pain behavior reinstated corneal hypersensitivity in injured mice but not in the sham control group. We suspect a similar phenomenon occurs in patients after ocular surgery. We propose a study that will build upon our findings to determine the effect of ocular surgery in a clinical setting. We will compare patients who have undergone either a scleral buckle (more invasive) or partial vitrectomy (less invasive) in one eye. Over the course of follow up visits for one year, we will qualitatively and quantitatively assess corneal sensitivity and severity of dry eye symptoms after administration of a mild irritant (5% hypertonic saline solution). We expect to see a larger proportion of patients develop increased corneal sensitivity and dry eye symptoms following the more invasive scleral buckle surgery than those who have undergone primary vitrectomy. We will also compare these patients with age-matched healthy controls who did not have ocular surgery.

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Abstracts

Poster Presentation #55

Abstract Title:	**Enhanced Patient-Provider Communication: Development of a Tool for Discussing Opioids and Non-pharmacologic Approaches to Pain**
Author(s):	K. Roper, Department of Family & Community Medicine, College of Medicine, U of Kentucky R. Cardarelli, Department of Family & Community Medicine, College of Medicine, U of Kentucky J. Jones, College of Medicine, U of Kentucky

Abstract: Objective: The primary objective of this study is to develop a communication tool that would guide the discussion between patients and their health care providers about pain treatment options. Hypothesis: Patients and providers view chronic pain management as a difficult topic of discussion. We hypothesized that patients and providers would cite specific factors as influences on this discussion: Lack of time, lack of information, and differences in treatment goals. Procedures: We searched AEHR of two physicians at the UK Turfland site for patients being treated for pain longer than 6 months. 60 eligible patients were identified, 30 were successfully contacted, and 11 were interviewed in two separate focus groups. (6 opioid users, 5 non opioid users) The Communication-Persuasion Matrix (CPM) framework was chosen to guide the framing questions for the moderator during the focus group sessions. Analysis: Results were analyzed by categorizing qualitative responses into the CPM framework. Additionally, quantitative responses were surveyed for each patient's most important treatment goals. These were pooled and analyzed for average and standard deviation of each variable. Findings: The patients' most cited reason for chronic pain management was improved activities of daily living (walking, climbing stairs, bending). The most problematic aspects of the discussion was lack of time, lack of presentation to alternatives, or a difference in treatment goals between patients and providers. Conclusions: A communication tool with questions required to be discussed at each chronic pain management visit, such as ADL, may save time and help guide this problematic conversation.

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Abstracts

Poster Presentation #56

Abstract Title:	**Progress towards developing zebrafish models to study the link between SoxC transcription factors and CHARGE syndrome**
Author(s):	L. A. Krueger, Department of Biology, U of Kentucky A.C. Morris, Department of Biology, U of Kentucky

Abstract: CHARGE syndrome (coloboma, heart defects, choanal atresia, growth retardation, genital abnormalities, and ear abnormalities) is a complex congenital genetic disorder resulting in severe defects in multiple organ systems with an occurrence of 1:8,000-10,000 live births. Mutations in chromodomain helicase binding protein 7 (CHD7) and defects in neural crest cell development and migration have been implicated in the pathogenesis of CHARGE syndrome, however the mechanisms underlying the ocular birth defects observed in CHARGE patients have not been identified. Our laboratory studies the development of the vertebrate visual system using zebrafish (Danio rerio). Previous work from our lab has shown that knockdown of Sox11, a member of the SoxC family of transcription factors, in zebrafish results in microphthalmia, coloboma, brain, trunk, and heart defects, all phenotypes observed in CHARGE syndrome. Furthermore, a duplication of Sox11 has been identified in a patient clinically diagnosed with CHARGE syndrome, and CHD7 has been shown to directly interact with Sox11 and Sox4 in neural stem cells. Taken together, these data strongly suggest that loss of SoxC expression contributes to the ocular and other phenotypes observed in Chd7-associated CHARGE syndrome. In this study, we begin to further investigate the role that Sox11 plays in the phenotypes seen in CHARGE syndrome by generating Sox11-mutant zebrafish using the CRISPR-Cas system. These experiments will provide a better understanding of the potential role of Sox11 in the pathogenesis of CHARGE syndrome.

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Abstracts

Poster Presentation #57

Abstract Title:	**Trauma Exposure, Trauma Symptoms and Perception of Research Participation in Children with Injury and Their Parents**
Author(s):	T. Borger, Department of Psychology, U of Kentucky C. Kindler, College of Medicine, U of Kentucky N. Kassam Adams, Children's Hospital of Philadelphia M. Marsac, College of Medicine, U of Kentucky

Abstract: Objectives: Despite a growing body of evidence that participation in trauma research is well-tolerated and even welcomed by children and parents, ethics boards may voice concerns about the nature of research activities for families with recent acute trauma exposure. This study adds to the literature by examining child and parent perceptions of participation in a study that included a parent-child observational task in the early aftermath of injury and tracking child and parent post-traumatic stress symptoms over time. Methods: 96 children (ages 8-12 years, M = 10.6) hospitalized for injury and one parent per child participated a 3-time point, longitudinal study. At baseline (within 2 weeks of injury), children and parents completed measures of self-reported PTSS and perception of research participation. PTSS measures were repeated at 6 and 12 weeks. Results: The majority of families reported that they were glad that they participated in the research study (61% children; 72% parents) and felt good about helping others by participating (74% children; 93% parents). Negative feelings were uncommon (< 10% of families). Parent and child perception of trust did not significantly correlate, but a small, significant correlation (r = .21) for positive appraisals emerged. Perceptions of research were not significantly related to child PTSS or parent PTSS at any time point. Conclusions: Results indicate that most individuals' research experience is positive, regardless of their trauma symptoms.

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Poster Presentation #58

Abstract Title:	**Neurodevelopmental Outcomes of Infants with Neonatal Opioid Withdrawal Syndrome are Compounded by Number of Additional Drugs Used During Pregnancy and Discharge Placement**
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Abstract: The national opioid crisis has led to an epidemic of Neonatal Opioid Withdrawal Syndrome (NOWS). The objectives of this study are to determine how maternal opioid use in combination with other substances affects outcomes of babies with NOWS and to determine the effect of foster care placement. This is a retrospective study of children followed at a regional care facility. The Bayley Scales III were administered at one year of age. 123 children had one-year assessments. Substance exposure included opiates alone vs opiates in combination with 1 or with 2-4 other drugs. These drugs included benzodiazepines, cocaine, marijuana, and others. The means (SD) of the language scores were 98.9 (1.6) for opiates alone, 93.3 (2.1) for additional 1 other drug, and 90.7 (2.5) for 2-4 other drugs (Kruskal-Wallis, p = 0.03). The means (SD) of the language scores were 90.9 (2.0) for foster care (n = 39), 98.5 (1.9) for kinship care (n = 48), and 96.9 (2.2) when discharged with mother (n = 34) (Kruskal-Wallis, p = 0.02). Results from ANCOVA analysis showed that the amount of drug exposures (p = 0.03) and who the baby went home with (p = 0.04) were independently significant, with no significant interaction (p = 0.27). Both the number of additional drugs and placement independently influenced language outcomes of babies with NOWS. Polysubstance use should be a consideration when treating women of child-bearing age with opiate dependence. This also portrays the importance of assuring that discharge environment will enhance the child's developmental potential.

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Poster Presentation #59

Abstract Title:	**The Cellie Coping Kit for Children with Injury: Initial Development and Planned Randomized Controlled Trial Protocol**
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Abstract: Purpose: Following pediatric injury, physical and psychological challenges may arise, often lasting beyond the course of medical intervention and negatively impacting recovery. The Cellie Coping Kit provides evidence-based coping techniques for children and their families post-injury. This presentation describes the systematic approach to the development of the coping kit as well as the ongoing randomized control trial designed to assess initial efficacy. Methods: The Cellie Coping Kit was created by reviewing literature and extracting strategies for managing injury-related challenges, undergoing expert review by a multidisciplinary team, and integrating feedback from children with injuries and their families. The current RCT plans to enroll 80 child-parent dyads, who will be randomly assigned to receive the intervention either at baseline (T1) or in 12 weeks (T3). All participants will complete follow-up measures at 6 week (T2), 12 week (T3), and 18 week (T4) intervals. Results: The resulting coping kit includes a toy named Cellie, a booklet for caregivers, and coping cards for children. The coping mechanisms are designed to address a range of social and emotional situations. Currently, 19 children (ages 8-12) and their caregivers have completed baseline assessments (T1) of coping strategies, health-related quality of life (HRQoL), and posttraumatic stress symptoms (PTSS). As the evaluation study is ongoing, we hypothesize that the Cellie Coping Kit will contribute to improvements in coping, HRQoL, and PTSS. Conclusions: Anticipated results would suggest that the Cellie Coping Kit may serve as an affordable intervention to promote emotional recovery and improve health outcomes in children following injury.

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Abstracts

Poster Presentation #60

Abstract Title:	**Promoting a Trauma-Informed Medical Care Framework among Pediatric Healthcare Professionals**
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Abstract: Background: Prior trauma exposure may affect patient-provider interaction and patient recovery, and medical professionals often experience trauma symptoms related to their work, leading to burnout. The effect of trauma exposure may be able to be mitigated through the implementation of trauma-informed care medical practice; TIC training programs are in their infancy. Objective: To evaluate the effectiveness of a new program promoting TIC with pediatric patients, families, and staff. The current study assesses proximal outcomes of healthcare professionals' confidence and knowledge in delivering TIC and longer-term outcomes of burnout and work satisfaction. Methods: 111 pediatric healthcare providers participated in a one-hour interactive seminar and completed measures on knowledge and confidence in delivering TIC (pre – T1/post – T2 training), burnout and work satisfaction (T1). Providers repeated these measures at a one-month follow up (T3; n = 41). Results: Preliminary results indicate a significant increase in TIC knowledge (e.g., delivery, self-care) from T1 to T2, which was maintained at T3. No significant changes were observed in burnout or work satisfaction from T1 to T3. Conclusion: Providing healthcare professionals with an integrated TIC framework may be effective in increasing their knowledge of and confidence in delivering TIC to patients; however, additional intervention may be necessary reduce provider burnout or improve work satisfaction.

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Poster Presentation #61

Abstract Title: **Pathologic Maternal Chorioamnionitis and Intermittent Hypoxemia in Preterm Infants**

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Abstract: Purpose: Intermittent Hypoxemia (IH) is defined as episodic drops in blood oxygen saturation. IH episodes have a cumulative effect on the occurrence of impairment and death in preterm infants. Inflammation worsens apnea and subsequently may increase IH. We wanted to test the hypothesis that infants born with prenatal inflammation due to maternal chorioamnionitis (MC) have increased IH during the first two months of life. Methods: A total of 134 infants < 34 weeks gestational age (GA) were enrolled. Patients were monitored with high resolution pulse oximeters to accurately assess IH. Primary IH measure was percent time spent/week with SpO2 below 80% (%time-SpO2<80). Presence of MC was collected from medical records and diagnosis was based on placental pathology. Results: Data was available for 134 patients (73 no MC, 19 MC, 42 MC and maternal funisitis). There was an overall increase in IH in infants with MC compared to no MC that was statistically significant beyond the 4th week of life. Unadjusted mean difference: wk 5, 0.33 $p<0.05$; wk 6, 0.40 $p<0.05$; wk 7, 0.25 $p=0.052$; wk 8, 0.32 $p<0.05$. Conclusion: Our results show that prenatal inflammation due to pathologic MC may be associated with persistent increased IH beyond the perinatal period; interesting finding documented for the first time in preterm infants.

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Poster Presentation #62

Abstract Title:	**Determining the Maternal Demographic Factors Involved in Non-Adherence to Infant Hearing Diagnostic Testing**
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Abstract: Introduction: Delayed diagnosis of pediatric hearing loss can cause significant delays in cognitive and social development. Objective: To elucidate maternal factors associated with non-adherence to recommended follow-up after an abnormal newborn hearing screening. Methods: Mother-child dyads were recruited for a randomized controlled trial in which one group was assigned a patient navigator and the other received standard-of-care. This study used the standard group to describe the demographic factors that influence delayed timing of the child's final hearing diagnosis. Results: Of the 53 participants, 45% received a final diagnosis by 3-months of age. Mothers of children without a diagnosis at 3 months were older (p= 0.04) and had more children (p=0.01) than the ones who received a final diagnosis. Of those without a timely diagnosis, 72% had at least one appointment before 3-months of age. Maternal age was the only significant variable in the univariate analysis. As maternal age increased in one unit the odds in favor of diagnosis decreased by 10% (OR: 0.9, 95% CI: .815, .98). Conclusions: Our findings indicate that older maternal age and higher number of children differ between groups and that only maternal age predicted timing of diagnosis. Moreover, no diagnosis by 3-months was not linked to total lack of compliance since 72% of those patients did attend an appointment within the recommended time frame. Systematic streamlining and interventions such as a patient navigation could help parents better understand the requirements of the diagnosis process to improve achieving a diagnosis during the first appointment.

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Abstracts

Poster Presentation #63

Abstract Title:	**Overcoming Barriers to a Randomized Clinical Trial: Understanding Opioid Exposed Infants and their Mothers**
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Abstract: Background and Objective: Neonatal Abstinence Syndrome (NAS) is the diagnosis given to infants experiencing withdrawal from opiate exposure in utero. This problem is on the rise, and it remains unclear how opiate treatment of NAS affects children's long-term developmental outcomes. The study goal is to determine whether clonidine treatment of NAS would result in a better neurobehavioral performance compared to morphine. Methods: This prospective randomized clinical trial (NCT03396588) is currently enrolling infants that are ? 35 weeks' gestational age, exposed to opioids, and admitted for treatment of NAS. Informed consent comes from the participants' mothers. Infants are scored using the Finnegan Neonatal Abstinence Scoring System and then randomized to receive morphine or clonidine if scores indicate need for treatment. Masked examiners will complete validated neurodevelopmental and neurobehavioral assessments throughout the first two years of life. A set of maternal surveys will further inform researchers on environmental and maternal factors that may influence childhood outcomes. Discussion: Barriers to any randomized, pharmacological clinical trial have potential to affect the outcomes if they are not properly addressed. Some of the barriers encountered in this study were anticipated and accounted for, while others have required adaptation along the way. These include but are not limited to the characteristics of patient population and systems issues. The research team remains intentional in its efforts to complete this ongoing study while maintaining fidelity.

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Abstracts

Poster Presentation #64

Abstract Title:	**Viral Pathogen-Specific Clinical and Demographic Characteristics of Children with Moderate to Severe Diarrhea in Mirzapur, Bangladesh**
Author(s):	A.E. Bray, College of Medicine, U of Kentucky G.J. Fuchs, Chief, Division of Pediatric Gastroenterology, U of Kentucky A.S.G. Faruque, International Centre for Diarrheal Diseases Research, Bangladesh

Abstract: Pediatric diarrheal disease is a leading cause of childhood morbidity and mortality worldwide, but particularly in low-income countries in sub-Saharan Africa and South Asia. The Global Enteric Multicenter Study (GEMS) examined the enteric etiologies as well as the demographics, socioeconomic markers, health-care seeking behaviors, and hand-washing practices of the households of children with diarrhea and their age and sex-matched controls in seven locations, including rural Bangladesh, over 3 years. This Bangladesh-specific study focused on viral enteropathogens (rotavirus, norovirus, adenovirus, astrovirus, and sapovirus) to evaluate pathogen-specific features of the disease burden. Rotavirus was the most prevalent pathogen, and use of shallow tubewell as the primary water source was positively correlated with this virus. Viral disease was most common in infants, with the exception of norovirus and sapovirus. The cost of treatment was highest for rotavirus as well, making it an obvious target for preventative measures and therapeutic interventions in combating viral diarrheal disease.

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Poster Presentation #65

Abstract Title:	**Mechanisms Underlying the Stimulatory Effect of Sulfur Dioxide on Rat Vagal Bronchopulmonary Sensory Neurons**
Author(s):	A. H. Lin, Department of Physiology, U of Kentucky R. L. Lin, Department of Physiology, U of Kentucky L. Y. Lee, Department of Physiology, U of Kentucky

Abstract: Chronic exposure to sulfur dioxide (SO2), an air pollutant, causes airway injury and debilitating airway diseases. Transient SO2 exposure triggers cough and reflex bronchoconstriction, indicating a stimulatory effect of SO2 on airway afferent nerves. Indeed, a recent study in our lab has demonstrated that vagal bronchopulmonary C-fibers are the primary target of inhaled SO2. This study aimed to investigate the underlying mechanism of this stimulatory effect of SO2 on bronchopulmonary C-fibers. Responses of single-unit fiber activities of these afferent nerves to the SO2 inhalation challenge (1000-2000 ppm, 10 breaths) were measured in anesthetized rats. Our preliminary results showed: 1) Inhalation of SO2 evoked a pronounced and reproducible stimulatory effect on pulmonary C-fibers. 2) Intravenous infusion of sodium bicarbonate raised the baseline arterial pH, which abolished the SO2-induced pulmonary C-fibers activation. 3) The stimulatory effect of SO2 was also blocked by amiloride (a blocker of acid-sensing ion channels, ASICs) and AMG8910 (an antagonist of transient receptor potential vanilloid type-1, TRPV1). To further investigate if this stimulatory effect is generated by a direct action of SO2 on sensory nerves, the change in intracellular Ca2+ concentration, [Ca2+]i, was measured in isolated rat vagal pulmonary sensory neurons. Perfusion with extracellular fluid saturated with SO2 (100, 200 and 400 ppm) evoked a significant increase in [Ca2+]i in a concentration-dependent manner in these neurons. In conclusion, our data suggested that inhalation of SO2 lowered the pH in airway/lung tissues, which generated the stimulatory effect on vagal bronchopulmonary C-fibers by activating both ASICs and TRPV1 channels.

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Abstracts

Poster Presentation #66

Abstract Title:	**Dendritic cells influence the altered neonatal CD8 T cell immunodominance hierarchy during influenza virus infection**
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Abstract: Neonates are more susceptible to influenza virus infection than adults, resulting in increased morbidity and mortality as well as delayed clearance of the virus. Previous work has indicated that decreased T cell and dendritic cell function underlies some of this vulnerability. We sought to understand CD8 T cell specificity and immunodominance during neonatal influenza infection as well as how any differences from the adult hierarchy might impact immunodominance and protection in subsequent infections. We found that neonatal C57BL/6 mice display an altered CD8 T cell immunodominance hierarchy, preferentially responding to an epitope in the influenza protein PA rather than the co-dominant adult response to NP and PA. Additionally, upon secondary infection, mice first infected as pups display inconsistent immunodominance and suffer increased morbidity compared to mice infected previously as adults. Finally, transfer of influenza infected adult dendritic cells to pups resulted in increased T cell activation and enhanced viral clearance as well as a slight induction of NP specific CD8 T cells. Taken together, these data suggest that infection early in life alters the specificity of memory responses to that pathogen and that dendritic cells may play a role in mediating this process. Additionally, vaccines targeting T cells should consider epitope usage and age specific dendritic cell physiology if the intended patient population includes infants as well as adults.

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Poster Presentation #67

Abstract Title:	**Inhibition of human metapneumovirus binding to heparan sulfate blocks infection in human lung cells and airway tissues**
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Abstract: Human metapneumovirus (HMPV), a recently discovered paramyxovirus, infects nearly 100% of the world population and causes severe respiratory disease in infants, the elderly, and immunocompromised patients. We previously showed that HMPV binds heparan sulfate proteoglycans (HSPGs) and that HMPV binding requires only the viral fusion (F) protein. To characterize the features of this interaction critical for HMPV binding and the role of this interaction in infection in relevant models, we utilized sulfated polysaccharides, HS mimetics and occluding compounds. Iota-carrageenan had potent anti-HMPV activity by inhibiting binding to lung cells mediated by the F protein. Furthermore, analysis of a minilibrary of variably sulfated derivatives of Escherichia coli K5 polysaccharide mimicking HS structure revealed that the highly O-sulfated K5 polysaccharides inhibited HMPV infection, identifying a potential feature of HS critical for HMPV binding. The peptide dendrimer SB105-A10, which binds HS, reduced binding and infection in an F-dependent manner, suggesting occlusion of HS at the target cell surface is sufficient to prevent infection. HMPV infection was also inhibited by these compounds during apical infection of polarized airway tissues, suggesting these interactions take place during HMPV infection in a physiologically relevant model. These results reveal key features of the interaction between HMPV and HS, supporting the hypothesis that apical HS in the airway serves as a binding factor during infection, and HS modulating compounds may serve as a platform for potential antiviral development.

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Abstracts

Poster Presentation #68

Abstract Title:	**Cough hypersensitivity induced by eosinophil granule-derived major basic protein in awake mice**
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Abstract: Nonasthmatic eosinophilic bronchitis is one of the major causes of chronic cough. Major basic protein (MBP), an eosinophil granule-derived cationic protein, is known to induce airway mucosal inflammation and bronchial hypersensitivity. However, little is known about the effects of MBP on cough sensitivity. Therefore, this study was carried out to determine the effect of MBP on modulating cough responses to inhalation of sulfur dioxide (SO2), an air pollutant and chemical irritant, in a murine model. Awake mice were each placed in a recording chamber that was ventilated with a constant flow (300 ml/min) of air or SO2 mixture. Coughs were detected by analyzing the pressure changes inside the chamber and in the intrapleural space (via telemetry), in conjunction with the audio and video signals recorded simultaneously. Cough responses to SO2 inhalation (300 and 600 ppm balanced in air) were determined for 5 days before and ~10 days after 0.02 mg of MBP instillation into the trachea of the mouse. Our preliminary data obtained in 4 mice showed: 1) inhalation of SO2 elicited cough responses in a dose-dependent manner; 2) after the administration of MBP, cough responses to both concentrations of SO2 were significantly elevated; 3) the cough hyperresponsiveness to SO2 reached the peak ~2 days after the MBP treatment, and returned to baseline after ~7 days. In conclusion, these findings suggest a possible role of MBP in the chronic cough associated with eosinophilic bronchitis.

Supported by: Filley WV, Holley KE, Kephart GM, Gleich GJ. Identification by immunofluorescence of eosinophil granule major basic protein in lung tissues of patients with bronchial asthma. Lancet 2: 11-16, 1982. Gu Q, Lim ME, Gleich GJ, Lee LY. Mechanisms of eosinophil major basic protein-induced hyperexcitability of vagal pulmonary chemosensitive neurons. Am J Physiol Lung Cell Mol Physiol. 296:L453-61, 2009. Zhang, Cheng, et al. 'Cough and expiration reflexes elicited by inhaled irritant gases are intensified in ovalbumin-Sensitized mice.' American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, vol. 312, no. 5, 2017.

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Poster Presentation #69

Abstract Title: **MANF Ameliorates Endoplasmic Reticulum Stress-induced Neuronal Damage**

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Abstract: Ethanol exposure during brain development causes profound damages to the central nervous system (CNS). The underlying cellular/molecular mechanisms are unclear. We have previously shown that ethanol exposure induces endoplasmic reticulum (ER) stress in the developing brain. Mesencephalic astrocyte-derived neurotrophic factor (MANF) is a neurotrophic and ER stress-responsive factor. The present study investigated the neuroprotective effects of MANF against ER stress-induced neuronal damage. We generated CNS specific MANF knockout mice, and compared tunicamycin (an ER stress inducer)-induced brain damage in wild-type and MANF-/- mice of early postnatal days. We also tested the protective effects of MANF against tunicamycin- and 1-methyl-4-phenylpyridinium (MPP+)-induced neuronal death in cultured human neuroblastoma (SH-SY5Y) cells using MTT assay. The effects of MANF on the expression level of ER stress-associated proteins were also investigated in vivo and in vitro using an immunoblotting assay. Here, we show MANF knockout significantly exacerbated tunicamycin-induced neuronal apoptosis in the developing brain, which is manifested by a drastic increase of cleaved caspase-3. Intriguingly, this neuronal damage is region specific; that is, cortex, hippocampus, and cerebellum have the most neuronal apoptosis. Pretreatment with 4-phenylbutyrate (4-PBA), an ER stress blocker, can reverse the effects of MANF deletion and rescue tunicamycin-induced neuronal death in the developing brain. Mechanistically, we showed MANF knockout reinforces tunicamycin-induced ER stress, which increases neuronal death. In vitro studies indicated that incubation with recombinant MANF protein (1-10 ng/ml) ameliorated tunicamycin- and MPP+-induced ER stress and neuronal death.

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Abstracts

Poster Presentation #70

Abstract Title:	**Whole exome sequencing in neonatal opioid withdrawal syndrome dyads**
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Abstract: Opioid abuse during pregnancy results in neonatal opioid withdrawal syndrome (NOWS) characterized by central, autonomic and enteric nervous system dysfunction. Mild NOWS is treated by therapeutic handling, while more severe NOWS is treated with opioids. In 2015, 18.6 % of all neonates born at Cabell Huntington Hospital were exposed to opioids in utero, however only half required pharmacological treatment, an incidence of 94/1000 live births (Loudin, 2017. J. Perinatology. 37: 1108.). To date, predicting which neonates will need treatment for NOWS is not possible. Studies focused on genes within opioid signaling pathways indicate that genetic profiles can predict addiction and withdrawal in adults and limited studies in the NOWS population have shown some associations. We hypothesize that NOWS intensity is in part due to variants in genes involved in maternal and neonate metabolism of opioids and in genes related to placental and brain development. In this study we compared the genetic profiles of maternal-neonate dyads based on the need to treat NOWS pharmacologically. Initial studies using a whole exome dyad approach, with a statistical model considering both maternal and neonatal genetic variants, indicate 37 maternal and 21 neonatal genetic variants significantly associated with the clinical response to opioids. Interestingly, more of these polymorphisms were seen in the dyads where the infant needed no treatment than the dyads where the infant required treatment. Further studies are required to determine if these polymorphisms are truly predictive and if they can potentially be used as therapeutic targets in this population.

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Poster Presentation #71

Abstract Title:	**Interactions of Social Reward and Opioid Reward in Adolescent Rats**
Author(s):	M. A. Avery Department of Psychology, U of Kentucky V. G. Weiss Department of Psychology, U of Kentucky M. T. Bardo, Department of Psychology, Center for Drug Abuse Research Translation, U of Kentucky

Abstract: Social interaction can act as a natural reward that activates cortical and mesolimbic reward systems in the brain. Previous studies have shown that social interaction can act as an alternative reward that competes with drug reward. While most of this research has been conducted using amphetamine (AMPH), the goal of this study is to determine if social interaction can act as an alternative to morphine (MORPH) due to their similar brain mechanisms. Adolescent male rodents were used because they find social interaction especially rewarding compared to adult males and females. A standard 10-day conditioned place preference (CPP) procedure was used with four groups assigned randomly as follows: (1) saline was conditioned against saline; (2) social interaction was conditioned against no social interaction (saline); (3) MORPH (5 mg/kg, s.c.) was conditioned against saline; and (4) MORPH was conditioned against social interaction. Results showed that Group 2 showed a preference for the peer-associated side over the saline side ($p<0.05$), evidence for social CPP. Additionally, Group 3 showed a preference for the MORPH-associated side, evidence for MORPH CPP, although it was only marginally significant ($p<0.06$). Most importantly, Group 4 showed no significant preference for either the MORPH- or peer-associated side, indicating that the rewarding effects of each stimulus (MORPH and peer) cancelled each other out. These results show that social interaction serves as an alternative for opiate reward, suggesting that promotion of prosocial behaviors during development may be a useful strategy for preventing the onset of opiate use disorder.

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Poster Presentation #72

Abstract Title: **A Preclinical Model for Socially-induced Cocaine Relapse**

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Abstract: Recovering addicts remain at high risk for relapse even after prolonged abstinence. To date, few candidate drugs have been effective at preventing relapse in clinical trials. This discrepancy between preclinical results and clinical outcomes suggests that current preclinical models of relapse may be overlooking key factors. For example, although rodent studies primarily focus on non-social factors, such as drug-associated cues or contexts, re-association with drug-using peers is a known trigger for relapse in humans. In the current study we sought to build a robust model of socially-induced cocaine seeking. Young male Sprague-Dawley rats learned to self-administer cocaine in the presence of the S+ peer and saline in the presence of the S- peer during separate twice-daily 60-min sessions, presented randomly. Infusions were paired with a 20-s timeout period signaled by the illumination of a cue light (CS). After 28 days of self-administration, they received 12 twice-daily 60-min extinction sessions (no peers or cues). Next, we tested drug-seeking across repeated reinstatement sessions, separated by extinction sessions, with responding elicited by a combination of peer (S+, S-, or none) and cue (CS present or absent). Initial results indicated poor discrimination between S+ and S- peers. By increasing the dose of cocaine and adding food pre-training we were able to demonstrate strong discrimination and robust reinstatement triggered by the S+ peer, but not by the S- peer or the CS. This effect was stable across repeated testing. This study provides a method for testing the effects of candidate pharmaceuticals on socially-induced drug seeking.

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Poster Presentation #73

Abstract Title:	**Social Influence on Remifentanil Self-Administration in Rats**
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Abstract: The initiation of drug taking in humans most often occurs in the presence of peers. In preclinical rat models, the use of modified operant chambers has allowed for the incorporation of social contact during self-administration sessions. These chambers feature two individual operant chambers separated by a wire mesh which allows for visual, olfactory, and some tactile contact. The current study used these chambers to assess the effects of social contact on remifentanil self-administration. It was hypothesized that paired rats would self-administer more remifentanil than rats with no social partners. Procedures: Adult male Sprague-Dawley rats (n=28) were randomly assigned to five different groups: three groups of paired rats (rats self-administering remifentanil paired with a partner self-administering remifentanil, rats self-administering remifentanil paired with a partner self-administering saline, and rats self-administering saline with a partner self-administering remifentanil) and two groups of rats with no social partners (rats self-administering remifentanil alone and rats self-administering saline alone). Self-administration data was collected through acquisition, increasing fixed-ratio requirements, and altering doses. Results: Linear mixed effects analysis indicated that there were main effects of group and session at all phases of self-administration (all $p<0.05$) as well as a session x group interaction during acquisition ($F(24,138)=3.46$, $p<0.05$). Post-hoc analyses examining rate of acquisition indicated that rats self-administering remifentanil paired with a saline partner acquired self-administration faster than the remifentanil alone group ($F(1,73=6.36$, $p<0.05$). Linear regression indicated that active lever configuration also significantly affected acquisition. When both active levers were close to the mesh divider, remifentanil-administering rats had a faster rate of acquisition compared to rats with active levers far from the mesh divider ($F(1,52)=20.60$, $p<0.05$). Conclusion: Paired rats acquired remifentanil self-administration more quickly than rats self-administering alone and the placement of the active lever could affect acquisition of self-administration.

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Poster Presentation #74

Abstract Title:	**Overdose Safety Household Assessment and Intervention**
Author(s):	A. K. Feiertag, College of Medicine, U of Kentucky C. A. Martin, Child and Adolescent Psychiatry, U of Kentucky

Abstract: Purpose: To provide an educational intervention for adolescents regarding household opioid overdose safety and assess their knowledge, attitudes, and awareness regarding this subject. Methods: Pre- and post-testing to analyze adolescents' knowledge, attitudes, and awareness regarding opioid overdose information pre- and post-intervention. Background: This project seeks to address the widespread, ever-increasing problem of opioid overdoses in Kentucky. Kentucky's death rate due to pharmaceutical opioid overdoses remains well above the national average – at least twice the national mortality rate since 2010. Beyond the issue of opioid overdoses lies a much bigger problem, which is the accessibility of these harmful substances, in addition to other seemingly innocuous pharmaceuticals, right inside our medicine cabinets. Dr. Catherine Martin and I dove directly into this issue, assessing potentially at-risk adolescents and their families regarding household opioid safety. Results: Knowledge, attitudes, and awareness regarding opioid overdoses increased significantly from pre-intervention to post-intervention in adolescents. Conclusions: Due to the multi-faceted nature of this problem, I hope to continue to address more aspects of the opioid overdose epidemic through other avenues. I have spoken bluntly about opioid overdoses in classrooms across Kentucky and demonstrated that adolescents will listen and care. Continuing to educate and bring awareness of resources to this unique population will facilitate discussion and learning among families throughout our state.

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Center for Clinical and Translational Science

Abstracts

Poster Presentation #75

Abstract Title:	**Posttraumatic Stress Symptoms Indirectly Effect the Relation Between Interpersonal Violence and Prescription Drug Misuse**
Author(s):	M. E. Bowen, Department of Psychology, U of Kentucky C. O. Hood, Department of Psychology, U of Kentucky C. L. Badour, Department of Psychology, U of Kentucky

Abstract: Background. Compared to other trauma types, individuals exposed to interpersonal violence (IPV) may be at risk for substance misuse. IPV exposure may indirectly relate to substance misuse through PTSD symptom clusters. Thus, this study examined whether IPV experiences were indirectly associated with prescription drug misuse via PTSD symptom clusters. Method and Hypotheses. Trauma-exposed college women (N=61; Mage=19.00, SD=1.22) responded to a cross-sectional survey that included questionnaires assessing interpersonal and non-interpersonal trauma exposure (Trauma History Questionnaire), PTSD symptoms (PTSD Checklist for the DSM-5), and prescription drug misuse in the past 6 months (Prescription Drug Misuse Questionnaire). We hypothesized that PTSD symptom clusters would have a significant indirect effect on the relationship between IPV experiences and prescription drug misuse. Results. The total effect of IPV exposure on past 6-month prescription drug misuse was not significant (path c: Nagelkerke R2=0.002, B=0.18, SE=0.61, p=.76). However, results revealed significant effects of PTSD arousal symptoms (B=0.17, SE=0.07, p=.01) and PTSD negative changes in mood and cognition (B=0.10, SE=0.05, p=.05) on prescription drug misuse. Indirect effects of IPV exposure on prescription drug misuse via PTSD arousal symptoms (B=0.64, SE=0.44, 95% BC CI [0.005, 1.71]) and PTSD negative changes in mood and cognition (B=0.60, SE=0.43, 95% BC CI [0.10, 1.63]) were significant. PTSD re-experiencing and avoidance symptoms were not significantly related to prescription drug misuse. Conclusion. This study offers preliminary evidence that IPV exposure is related to prescription drug misuse, in part, by way of specific PTSD symptoms clusters.

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Poster Presentation #76

Abstract Title:	**Profile of Methamphetamine Users in Corrections-Based Substance Abuse Programs**
Author(s):	M. G. Davis, College of Social Work, U of Kentucky E. Winston, Center on Drug and Alcohol Research, U of Kentucky M. Staton, Department of Behavioral Science, U of Kentucky K. Pangburn, Department of Corrections

Abstract: Rates of reported methamphetamine use have almost doubled since 2012 (48.5% vs 23.5%). Increasing rates of use along with dangerous associated side effects suggest the need for increased awareness and attention to this group. This presentation describes the characteristics of individuals who participated in substance abuse treatment in prisons, jails, and community settings who have reported methamphetamine use during the 12 months prior to incarceration compared to those who did not report methamphetamine use. This analysis uses secondary data collected as part of the Criminal Justice Kentucky Treatment Outcome Study during the baseline assessment for individuals entering substance abuse programs from March 2016 through February 2018 (N=11,886). Analysis focused on differences in demographics, criminal history, substance use, and mental and physical health among methamphetamine users (n=5,769) and those who did not report methamphetamine use (n=6,117). Methamphetamine users were predominately white (95.6%) males (82.2%) with an average age of 34.1, and were more likely to live in a non-metropolitan area (53.5%). This population also reported significantly higher depression (49.4% vs 38.1%, p<.001), anxiety (53.8% vs 45.1%, p.<.001), and suicidal thoughts (15.8% vs 9.9%, p<.001) as well as significantly higher use of other illicit drugs. Methamphetamine users were almost twice as likely to have ever injected drugs (64.1% vs 34.9%, p<.001). Findings suggest that methamphetamine users may have unique treatment needs due to increased reporting of mental health symptoms. Future research should focus on interventions and specific risk factors associated with the rise in methamphetamine use.

Supported by: Commonwealth of Kentucky, Department of Corrections

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Abstracts

Poster Presentation #77

Abstract Title:	**Upper extremity soft tissue infections among IV drug users: A healthcare utilization and cost analysis study**
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Abstract: Background: Soft tissue infections are among the leading causes of emergency department (ED) and inpatient resource utilization in the intravenous drug user population. Several studies have sought to quantify healthcare utilization and costs from soft tissue infections in this cohort; however, this data is limited. We suggest that IV drug users (IVDUs) with upper extremity soft tissue infections(UESTIs) have higher medical costs and healthcare utilization than their non-IVDU counterparts. Methods: A retrospective double cohort study (2006-2015) was conducted at the authors' institution. Adult patients age 18-75 with UESTIs including those with suspected IVDU were included. The EPSi database was queried using a combination of ICD drug abuse and CPT codes associated with management. A total of 3,277(non-IVDU n=2,913, IVDU n=364) ED visits for 2,744 unique patients were identified. Additionally, the KMSF database was analyzed in order to determine costs and healthcare utilization. Statistical analyses were performed using Chi-square, Fisher's exact, t-test or Mann-Whitney U. Results: IVDUs had significantly higher total costs than their non-IVDU counterparts ($2,795 vs. $257, p <0.0001). Differences in costs were primarily driven by increased median length of stay (2 days vs. 0, p<0.0001) and additional laboratory costs. The IVDU cohort was also more likely to be uninsured or a Medicaid beneficiary, and had higher admission rates (p<0.0001). Conclusion: UESTIs in IVDUs place a significant economic burden on our healthcare system. Future efforts should focus on healthcare policy, legislation and harm reduction strategies aimed at lowering the economic burden these infections have on our system.

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Poster Presentation #78

Abstract Title:	**'I Can Do This.' : Pre-Treatment Expectations and Post-Treatment Outcomes Among KY Offenders Enrolled in Corrections-Based Substance Abuse Treatment.**
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Abstract: Treatment approaches for offenders have demonstrated successes, but research is limited on the influence of individuals' abstinence self-efficacy and treatment outcomes. Self-efficacy gives insight into an individual's belief of their ability to change. This presentation describes how predictions of one's ability to stay off drugs and alcohol prior to entering a corrections-based substance abuse program is associated with relapse rates in the 12-month period post release. This analysis includes secondary data collected as part of the Criminal Justice Kentucky Treatment Outcome Study. Data was collected during baseline for individuals entering Kentucky Department of Corrections substance abuse treatment programs and follow-up data was collected 12 months post release from July 2015 to June 2016 (N=350). At baseline, 81.1% (n=284) of participants reported having "positive" efficacy expectations of their chances to stay off of drugs and alcohol, while 18.9% (n=66) reported having "negative" efficacy expectations. "Positive" efficacy expectations includes reports of moderately good or very good chances; "negative" efficacy expectations include very poor, moderately poor, or uncertain responses. At follow-up, those who did not report relapse were more likely to report positive expectations of their abstinence ability (86.4%, $p<0.05$) at baseline. Findings suggest that an individual's efficacy expectations of their ability to remain clean is an important factor in staying sober post treatment. Treatment programs may consider incorporating self-efficacy development in their clients in order to increase outcomes. Further research should focus on what other variables along with self-efficacy may be related to relapse rates.

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Poster Presentation #79

Abstract Title:	**Re-evaluating Bupropion as a Therapeutic for Stimulant Use Disorders Using Retrospective Analysis of Health Claims Data**
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Abstract: Misuse of stimulants, including cocaine and amphetamines, is a pervasive public health problem exacerbated by the fact that there are no pharmacotherapies approved to treat stimulant use disorders (StUDs). Health claims are a burgeoning resource to evaluate pharmacotherapies with potential for drug repurposing, which is the identification of novel indication(s) for existing medications. As an exemplar of using health claims data to evaluate medications for repurposing, we assessed the association between bupropion (due to its putative potential as an agonist replacement therapy) and StUD remission. Using?the Truven Marketscan database, we identified 98,978 individuals (65% male, average age 33.4 years)?with a?StUD.?Logistic regression was used to model the association between bupropion and remission (n=833) while controlling for age, sex, utilization, type/severity of StUD, and comorbid mood disorders. Individuals who filled a prescription for bupropion within 30 days of their first StUD diagnosis were 2.5 times (95% confidence interval: 1.74-3.54) more likely to receive a remission diagnosis than their counterparts. Sex and history of mood disorders acted as effect modifiers, such that bupropion increased likelihood of remission only in males and individuals without a history of depression. Our results from this big data approach suggest that bupropion may improve StUD outcomes in a subset of individuals and future research should re-visit the use of bupropion for specific individuals with StUDs. Importantly, this work provides a framework for leveraging health claims to evaluate medications with potential to be repurposed.

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Abstracts

Poster Presentation #80

Abstract Title: **Parental Drug Abuse: The Effect of Drug Abuse on Parenting Activities**

Author(s): K.M. Kelly, Center of Drug and Alcohol Research
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Abstract: Background & Purpose: Over the last couple decade's parental substance abuse as became a significant factor of children being placed in out-of-home care including foster care and family placement. Children who have parents who abuse drugs are three times more likely to be neglected than children who come from non-substance abusing families. This leads to a total of 2/3 of all neglect cases to involve some degree of substance abuse. The overall aim of the study is to describe the parenting activities in rural women drug users. Method: This study involved random selection, screening, and face-to-face baseline interviews with 400 women substance users in rural jails in one Appalachian state. Descriptive analyses focus on parenting, custody status, and parenting behaviors. Results: Rural women drug users in this study were about 33 years old, mostly white(99%), and most had children(87%). Among women with children, 53.3% reported having a case with child services in the past, and 17% reported having an open case. Parenting activities included 76.7% reporting spending 30 minutes or more a week playing with their children. 63.3% took their children to an organized activity, and 63.3% had read a book to their child in the week following incarceration. Discussion: Based upon the findings of this study over half of the 400 participants recruited reported having lost custody of their children indicating a negative effect of substance abuse on parenting activities. The participants who have custody or spent time with their children reported a median of 25 hours of quality time with that child a week indicating drug use to not be a factor in their parenting activities.

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Poster Presentation #81

Abstract Title:	**Awareness and Perceptions of Syringe Exchange Programs in Kentucky**
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Abstract: Background: Syringe exchange programs (SEPs) provide many health benefits for persons who inject drugs and their communities, including reduced transmission of blood-borne illnesses, safe disposal of used syringes, and opportunities for treatment referral. Beginning in March of 2015, public health departments across Kentucky began offering SEP services through the passage of Kentucky Senate Bill 192. As services expand state-wide, research is needed to understand awareness and perceptions associated with facilitating factors and barriers to accessing SEP services. Methods: Data were collected from 147 individuals who had participated in corrections-based substance abuse treatment programs in Kentucky, one year after their release to the community, as part of an ongoing KY Department of Corrections state-funded evaluation. Awareness of SEPs in the state was examined in relation to sociodemographic variables and substance use history, and qualitative responses related to SEP perceptions were coded based on emergent themes. Results: Past-year self-reported heroin use at treatment entry was the only variable which was significantly related to awareness of SEPs existing in Kentucky. Qualitative analysis indicated that while participants were generally knowledgeable about SEP benefits, concerns for privacy (fear of being recognized by other users or community members, or of consequences from law enforcement) were discussed as a potential barrier to SEP utilization. Discussion: Less is known about large-scale, state-wide implementation of SEP programs. Results suggest that as SEP services expand in Kentucky, communities should continue to receive outreach and education about local SEP services and benefits, including protections for client confidentiality.

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Poster Presentation #82

Abstract Title:	**The Bayesian Method for Confounding as Applied to Personality and Substance Use Data to Estimate Average Causal Effect**
Author(s):	L. Su, College of Medicine, U of Kentucky C. Wang, Department of Biostatistics, U of Kentucky C. Lee, Department of Psychology, U of Kentucky R. Milich, Department of Psychology, U of Kentucky D. Lynam, Department of Psychology, Purdue U

Abstract: Purpose: To investigate possible correlations between substance use and personality trait measurements in students attending the University of Kentucky using the Bayesian Adjustment for Confounding. Methods: The analysis was done in the statistical analysis software R using the Bayesian Adjustment for Confounding as developed by Dr. Chi Wang et al. The resulting model related the personality trait measures with substance use while accounting for a multitude of confounders. Data/Results: There were 449 individuals in the data. The dataset contained 10 different personality measurements from two different models. These variables were the exposure variables. The four outcome variables used were frequency of alcohol use, frequency of marijuana use, frequency of tobacco use, and audit total score, a measure of how harmful the subject's alcohol use is. 37 confounders were also included in the model, including sex, race, age, and quite a few variables involving the subject's friends' usage and opinions of alcohol, marijuana, and stimulants. This resulted in evaluating 40 associations/relationships, each relating one exposure variable to one outcome variable. The results showed which confounders were selected often in each model. The average causal effect (ACE) was also calculated from the models, providing a measurement of the actual level of causation between the two variables. Conclusions: Overall, the Bayesian Adjustment for Confounding is a method useful for eliminating confounders in observational studies and establishing causation with more certainty. The relationship that showed the highest positive effect was between positive urgency and audit total score. The relationship showing the most negative effect was between conscientiousness and audit total score. An example of a relationship with no effect was between marijuana use frequency and extraversion. Through the BAC method, the direct effects of personality traits on substance use can be accurately estimated.

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Poster Presentation #83

Abstract Title:	**Evaluating Electronic Cognitive Behavioral Therapy to Reduce Insomnia, Sleep Aid Use, and Stress in Appalachian Women Ages 45+**
Author(s):	M.E. Moloney, Department of Sociology, U of Kentucky

Abstract: Background: Stress-induced, transient sleeplessness is often diagnosed as insomnia and treated with sleep aids including sedative hypnotics (SH). SH pose myriad health risks (e.g., falls, cancer, neurocognitive disorders). These risks are of particular concern to women ages 45+, especially Appalachian women (AW). AW experience multiple economic and psycho-social stressors, have high rates of insomnia and SH use, and fragmented healthcare access. This population would likely benefit from an accessible, non-pharmacologic insomnia therapy, such as electronic cognitive behavioral therapy for insomnia (e-CBT-I). Objective(s): We are assessing feasibility, efficacy, and acceptability of SHUTi (Sleep Healthy Using the Internet), a well-validated e-CBT-I program in AW ages 45+ (N=40). Methods: Participants are AW ages 45+ with Internet access who experience insomnia (3+ months) and use sleep aids. SHUTi is comprised of 6, once-weekly online educational sessions (~40-60 minutes) and a daily online sleep diary (~2-3 minutes). Pre- and post-intervention participants complete an online survey and semi-structured qualitative interview to assess sleep, SH use, stress, and SHUTi acceptability. We will use grounded theory to analyze qualitative data. Multi-level modeling will be used to assess changes over time in quantitative data. We hypothesize that SHUTi will increase sleep latency while decreasing stress and SH use. Results: Data collection is ongoing. We have 40 participants enrolled; 10 have completed the SHUTi program. Conclusions: This innovative pilot project is a first step in determining if a scalable, community-accessible, non-pharmacologic intervention may improve sleep, reduce stress and SH use, and ultimately protect health in AW ages 45+.

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Poster Presentation #84

Abstract Title:	**RNA-seq and Histological Characterization of Human Peripheral Nerve Tissue Used in Brain Grafts for the Treatment of Parkinson's Disease**
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Abstract: Currently two clinical trials (NCT01833364 and NCT02369003) are underway which feature the implantation of a peripheral nerve autograft to the brain (targeted to the Substantia Nigra) in combination with Deep Brain Stimulation (DBS) for the treatment of patients with Parkinson's disease. As of 1/8/2018, 46 patients have received a graft. This nerve tissue is harvested from the sural nerve, a cutaneous sensory nerve located in the lateral ankle, from patients undergoing DBS surgery. The tissue receives a conditioning injury -in situ two weeks prior to grafting. This study aims to characterize the effect of this conditioning. Two sural nerve tissue samples (pre-conditioned and post-conditioned) per patient were collected from six patients during DBS surgeries 14 days apart. RNA sequencing (RNA-seq) was used to measure absolute and relative levels of gene transcripts in the pre-conditioned and post-conditioned nerve tissue. These findings were supplemented by histology of the nerve tissue. The results of these experiments show: 1) Consistent similarity within the pre-conditioned and post-conditioned group transcriptomes 2) Consistent changes between the pre-conditioned and post-conditioned group transcriptomes 3) Increased transcript levels related to nerve repair, growth factor production, and immune cell migration pathways 4) Decreased transcript levels related to myelin production pathways, consistent with the repair Schwann cell phenotype. All results are statistically significant ($p < 0.05$ and $q < 0.05$). These findings suggest that the nerve graft tissue implanted in human patients has a pro-regenerative phenotype which has the potential to alter the course of neurodegeneration in the brain.

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Abstracts

Poster Presentation #85

Abstract Title: **Role of Visceral Adipose Tissue in the Development of Sepsis**

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Abstract: Adipose tissue is known to be an important contributor to chronic inflammatory diseases. Using a murine model, we previously reported that visceral adipose tissue is also highly active during severe acute inflammation and is a major source of cytokines and thrombotic factors during experimental sepsis. The objective of this study was to test the hypothesis that removal of visceral adipose tissue would improve the response to experimental sepsis. Sepsis was induced via cecal slurry (CS) injection in a group of mice (n=10), of which a subset had been subjected to surgical removal of visceral adipose tissue (n=5), while the rest underwent a sham procedure (n=5). After CS injection, mice with visceral adipose tissue removed experienced more profound hypothermia (30.4 ± 0.8°C vs 33.5 ± 1.0°C at 6h, p=0.04), higher plasma IL-6 concentration (220 ± 70 pg/µL vs 70 ± 30 pg/µL at 6h, p=0.03), elevated creatinine levels (1.5 ± 0.2 mg/dL vs 0.9 ± 0.1 mg/dl at 24 h, p=0.02)), and higher circulating bacterial counts (2400 ± 700 vs 400 ± 100 at 48 h, p=0.02). These findings suggest that the absence of visceral adipose tissue exacerbated sepsis. The disparity between the findings and our hypothesis are potentially explained by a proposed mechanism through which adipose tissue traps bacteria, preventing it from entering the circulation. Thus, in this experimental setting, the benefits of the adipose tissue (bacteria trapping) seemed to outweigh the consequences (inflammatory mediator production). Future studies incorporating antibiotic treatment during sepsis induction will test this possibility.

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Poster Presentation #86

Abstract Title:	**Cost Evaluation of Enhanced Recovery After Surgery Protocol for Open Ventral Hernia Repair**
Author(s):	C. Harryman, M. A. Plymale, E. Stearns, C. Tancula, D. L. Davenport, W. Cheng, J. S. Roth

Abstract: Introduction: A comprehensive Enhanced Recovery after Surgery (ERAS) protocol for open ventral hernia repair (VHR) is associated with improved clinical outcomes including more rapid return of bowel function and reduced infections. The purpose of this study was to evaluate cost of ERAS implementations and postoperative care compared to a pre-ERAS cohort. Methods: With IRB approval, clinical characteristics and post-operative outcomes data were obtained via retrospective review for patients 2 years prior and 14 months post ERAS implementation. Hospital costs were obtained from cost accounting system inclusive of initial hospitalization and 180 days postoperatively. Clinical data and hospital costs were compared between groups. Results: 178 patients (127 pre-ERAS, 51 post-ERAS) were identified. Pre-operative and operative characteristics - including gender, ASA class, co-morbidities, BMI - were similar between groups. Quicker return of bowel function (p=0.001) and decreased incidence of superficial surgical site infection (p=0.003) were seen in ERAS patients. No significant difference in hospital readmission and length of stay were found. Inpatient pharmacy costs were increased in ERAS group ($2,673 vs. $1,1176 p=<0.001) but total hospital costs (14,692 vs 15,151, p=0.538) were less in the ERAS group and other costs were similar. Discussion: Standardization of care via the ERAS protocol increased inpatient pharmacy costs without increasing total costs of care, and improved clinical outcomes. Further care adjustments based on study findings will be evaluated in an effort to reduce length of stay and further reduce costs.

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Poster Presentation #87

Abstract Title:	**The Use of Human Amnion/Chorion Membrane and Umbilical Cord Grafts for Treatment of a Scalp Wound with Exposed Bone**
Author(s):	E. H. Campbell, College of Medicine, U of Kentucky M. J. Zalla, Dermatology, College of Medicine, University of Cincinnati and Dermatology Associates of Northern Kentucky

Abstract: Introduction: Healing of wounds with exposed bone can be challenging, and options for repair are limited. We report the first case of the use of dehydrated human amnion/chorion membrane and umbilical cord grafts to treat a scalp wound with exposed bone following Mohs surgery. This new technology provides an additional option for scalp wounds that cannot be closed primarily or with local flaps and may alleviate the need for surgical manipulation of bone to stimulate granulation. Case report: An 89-year-old man presented with a 5.0 x 4.9 cm squamous cell carcinoma of the frontal scalp. He underwent Mohs excision, resulting in a 4.1 cm x 3.0 cm area of exposed bone. A dehydrated human amnion/chorion membrane (dHACM) graft (EpiFix®) was then placed in an effort to stimulate granulation. After two weeks, fibrin slough and focal central buds of granulation tissue were noted; no exposed bone was visible. By 9 weeks, the wound was healed completely without complications. Discussion: Scalp wounds with exposed bone can heal with traditional conservative wound care but tend to be slow and may never heal completely. The fact that this wound granulated completely by three weeks suggests a beneficial effect of the dHACM. Advantages to this novel approach include the ease of grafting, expedited granulation and healing time, and lack of pain, immune reaction, or wound care. Conclusion: We report the first case of human amnion/chorion membrane and umbilical cord grafts for treatment of a Mohs surgical defect with exposed bone.

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Center for Clinical and Translational Science

Abstracts

Poster Presentation #88

Abstract Title: **Appendicitis Grade Predicts Operative Duration and Hospital Costs**

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Abstract: Introduction: Recently, the American Association for the Surgery of Trauma (AAST) sought to establish an explicit grading system for 16 emergency general surgery (EGS) disorders. The goal of the AAST grading system was to allow for more accurate prediction of risk and outcome, to assist in improvement of quality and resource management, and to provide a framework for research studies. The AAST grading system is based on previously existing grading systems, literature review, and expert opinion and includes clinical, imaging, operative, and pathologic criteria but has not been completely validated. A previous study reported a correlation between AAST grade of appendicitis and duration of hospital stay, occurrence of postoperative complications, and need for conversion to open procedure while operating. Our aim was to expand upon this and validate the AAST grading system for appendicitis based upon duration of symptoms, operative duration, hospital costs and revenue. Methods: A retrospective medical record review of all patients older than 8 years old who underwent emergent appendectomies after presenting with acute appendicitis was performed working backwards from December 2016 until at least 40 of each grade of appendicitis were reviewed. Appendicitis severity was determined using the criteria of the AAST grading scale (I-V), with V being the most severe. Statistical comparisons were made between increased severity and duration of symptoms, operative duration, hospital costs and revenue. Data were analyzed using ANOVA or chi-square tests as appropriate. Results: A total of 1099 appendectomies performed between August 2013 and December 2016 were analyzed, including: grade I 676 (61.5%); II 190 (17.3%); III 132 (12.0%); IV 61 (5.6%); and V 40 (3.6%). Patients had a median age of 18 (range 8-85) and 44.4% were female. Patients with increasing AAST grade had a longer duration of symptoms ($p < .001$), longer operative duration ($p < .001$), increased direct costs ($p < .001$) in every category measured (OR, pharmacy, imaging, lab) and contribution margin, indirect cost and profit ($p < .001$). Conclusion: AAST appendicitis grade is a valid predictor of disease severity, technical difficulty, hospital cost and revenue. Furthermore, duration of symptoms predicts severity of appendicitis as measured by AAST grade. These data provide objectivity to operative difficulty and resource utilization for this common diagnosis that can be used in clinical care, residency training and policymaking.

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Abstracts

Poster Presentation #89

Abstract Title:	**Outcome of Patients with Small Vessel Vasculitis after Renal Transplantation: National Database Analysis**
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Abstract: Small vessel vasculitis (SVV) and anti-glomerular basement membrane (GBM) disease commonly affect the kidney and can progress to end stage renal disease. The goal of this study is to compare outcomes of patients who received a renal transplant as a result of SVV and anti-GBM disease (group A) to those who received kidney transplants because of other causes (group B). This is a retrospective analysis of United Network for Organ Sharing registry data for adult primary kidney transplants from January 2000 to December 2014. Group A patients (N=2196) were compared to a group B (N=6588); groups were case matched for age, race, gender, donor type, and year of transplant in a 1:3 ratio. Renal and patient survivals were better in the group A ($p<0.001$). New onset diabetes after transplant developed in 8.3% of the group A and 11.3% of group B ($p<0.001$). Seventeen patients in group A developed recurrent disease (0.8%). Group A patients had significantly higher risk of developing post-transplant solid organ malignancies (11.3% vs. 9.3%, $p=0.006$) and lymphoproliferative disorder (1.3% vs. 0.8%, $p=0.026$). Independent predictors of graft failure and patient mortality were recipients' morbid obesity, diabetes, age, and dialysis duration (HR of 1.7, 1.4, 1.1/10-year, and 1.1/year for graft failure, and 1.7, 1.7, 1.6/10-year and 1.1/year for patient mortality, respectively). Renal transplantation in patients with SVV and anti-GBM disease has favorable long-term graft and patient outcomes with a low disease recurrence rate. However, they may have a higher risk of developing post-transplant malignancies.

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Abstracts

Poster Presentation #90

Abstract Title:	**Assessment and Treatment of Behavioral Disorders in Children With Hearing Loss: A Systematic Review**
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Abstract: Objective: There is evidence that children who are deaf and hard of hearing (DHH) have a higher incidence of behavioral disorders. Assessment of behavioral health in this population is often complicated by language developmental delays, which may result in unrecognized and untreated behavioral problems. The purpose of this study is to assess the association of behavioral disorders with pediatric hearing loss and explore behavioral interventions for children in this population. Data Sources: PubMed, CINALH, PsychINFO, and Web of Science. Review Methods: Search terms included: problem behavior, child behavior disorders/diagnosis, child behavior disorders/psychology coupled with hearing loss, cochlear implants, hearing aids, or deafness. Studies from the last thirty years (1985-2016) were included. The articles were reviewed independently by three reviewers. Results: This review found 46 articles that met criteria and 25 found an association of behavioral problems (both externalizing and internalizing behaviors) in children with hearing loss compared with normal hearing children. Only 4 of 12 studies found a significant association regarding parental stress regarding child behavior in parents of children with hearing loss. There was limited evidence regarding interventions to address behavioral disorders in DHH children. Conclusions: There is a significant body of evidence demonstrating an association between behavioral problems and hearing loss and children but a lack of clear understanding of the mechanisms involved. There is limited evidence on interventions to address behavioral problems in DHH children. Future research is warranted to mitigate long-term effects of disruptive behavior in these children.

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